Epilepsy-related and other causes of mortality in people with epilepsy: a systematic review of systematic reviews

Journal Pre-proof

Epilepsy-related and other causes of mortality in people with epilepsy: a systematic review of systematic reviews

Gashirai K. Mbizvo, Kyle Bennett, Colin R. Simpson, Susan E. Duncan, Richard F.M. Chin

PII: S0920-1211(19)30280-3

DOI: https://doi.org/10.1016/j.eplepsyres.2019.106192

Article Number: 106192

Reference: EPIRES 106192

To appear in: *Epilepsy Research*

Received Date: 6 May 2019

Revised Date: 15 August 2019

Accepted Date: 25 August 2019

Please cite this article as: Mbizvo GK, Bennett K, Simpson CR, Duncan SE, Chin RFM, Epilepsy-related and other causes of mortality in people with epilepsy: a systematic review of systematic reviews, *Epilepsy Research* (2019), doi: https://doi.org/10.1016/j.eplepsyres.2019.106192

Title: Epilepsy-related and other causes of mortality in people with epilepsy: a systematic review of systematic reviews

Authors: Gashirai K Mbizvo[a], Kyle Bennett[a], Colin R Simpson[b,c], Susan E Duncan[a,d], Richard FM Chin[a,e]

[a] Muir Maxwell Epilepsy Centre, Centre for Clinical Brain Sciences, The University of Edinburgh, Edinburgh, UK

[b] Faculty of Health, Victoria University of Wellington, Wellington, NZ

[c] Usher Institute of Population Health Sciences and Informatics, The University of Edinburgh, Edinburgh, UK

[d] Department of Clinical Neurosciences, Western General Hospital, Edinburgh, UK

[e] Royal Hospital for Sick Children, Edinburgh, UK

Corresponding Author

Dr Susan Duncan - Muir Maxwell Epilepsy Centre, University of Edinburgh, 20 Sylvan Place Edinburgh, EH9 1UW, UK

Tel: +44 (0) 131 536 0801, Fax: N/A

Email: susanxduncan@gmail.com

Other Author Email Contact

Gashirai Mbizvo – gashiraimbizvo@hotmail.com

Kyle Bennett – kyle-bennett@hotmail.co.uk

Colin Simpson – c.simpson@ed.ac.uk

Richard Chin – rchin@exseed.ed.ac.uk

Highlights

- Mortality in epilepsy has remained high and virtually unchanged since the 1950s
- Epilepsy-related mortality predominates causes of death in people with epilepsy
- Sudden unexpected death in epilepsy (SUDEP) is a common epilepsy-related cause of death

- Other common epilepsy-related causes include alcohol, drowning, pneumonia, and suicide
- The epilepsy-related cause of death most extensively investigated for risk factors is SUDEP

Abstract

Background: This systematic review of epilepsy mortality systematic reviews evaluates comparative risks, causes, and risk factors for all-cause mortality in people with epilepsy (PWE) to specifically establish the burden of epilepsy-related deaths.

Methods: MEDLINE and Embase were searched from conception to 26/12/2018 for systematic reviews evaluating all-cause mortality in PWE of any age. Independent study selection, data extraction and quality assessment were performed. Deaths were separated into epilepsy-related and unrelated using a recently published classification system. Outcomes included standardized mortality ratio (SMR) and mortality rate (MR) in a primary analysis of comparative risks, causes, and risk factors for all-cause and epilepsy-related mortality. A narrative synthesis of review findings was used to present results, including from a secondary analysis individual epilepsy-related death risk factors.

Results: Six moderate/high-quality systematic reviews were included in the primary analysis, evaluating 103 observational studies. All-cause mortality remained similarly high between 1950–present (median SMR range 2.2–3.4). Africa had the highest SMR (median 5.4, range 2.6–7.2). SMRs were also higher for children < 18 years (median 7.5, range 3.1–22.4) than adults (median 2.6, range 1.3–8.7), and for epilepsy-related (median 3.8, range 0.0–82.4,) than unrelated causes (median 1.7, range 0.7–17.6). Structural brain disease conferred the greatest risk for all-cause mortality (SMR range 24.0–41.5). Common epilepsy-related causes included alcohol, drowning, pneumonia, and suicide. In secondary analysis of nine additional systematic reviews, epilepsy-related death risk factors were reported for sudden unexpected death in epilepsy, drowning and suicide.

Conclusions: Premature all-cause mortality remains a major problem in PWE globally, particularly in children and young adults, with most being epilepsy-related and potentially preventable. SUDEP is only one of several other common and important epilepsy-related causes of death.

Keywords: SUDEP; Death; Seizures; Overview of reviews; Cohort study; Case-control study

1. Introduction

There are 70 million people with epilepsy (PWE) worldwide, and epilepsy contributes to 0.7% of the global burden of disease (Fazel et al. 2013; Mbizvo et al. 2012). Although PWE are subject to the same causes of death as the population without epilepsy, mortality in PWE is greater because they also die of epilepsy, its treatment, or its comorbidities: so-called "epilepsy-related deaths" (Devinsky et al. 2016). Avoidable deaths in PWE tend to be those that are epilepsy-related because the greater risk of death over the general population is abolished by, for example, achieving seizure freedom through establishing effective treatment strategies (Neligan and Sander 2011; Neligan A and Bell GS 2009). However, primary studies and systematic reviews reporting mortality in PWE are yet to focus on epilepsy-related mortality *specifically* perhaps because until the recently published Call to Action in recognizing and preventing epilepsy-related mortality by Devinsky et al. (Devinsky et al. 2016), there were no systematic methods for classifying the deaths in PWE into those that are most likely to be epilepsy-related. We have now capitalized on these methods by conducting a systematic review of the systematic reviews that have investigated mortality in PWE in order to ascertain: 1) the quality of individual systematic reviews; 2) the rate and comparative risks for all-cause mortality; 3) causes of death and the proportion that are epilepsy-related; and 4) risk-factors for all-cause and epilepsy-related mortality. We took the novel approach of classifying the data according to whether or not deaths were likely to be epilepsy-related using this recent Devinsky classification system (Devinsky et al. 2016) (table 1). We also aimed to elucidate the relevant areas for future research.

Table 1: Classification of epilepsy-related deaths by Devinsky (Devinsky et al. 2016)

Deaths directly due to epilepsy	➢ SUDEP ➢ Status epilepticus ➢ Drowning ➢ Car accidents ➢ Falls ➢ Burns ➢ Other seizure-related accidents
Deaths due to acute symptomatic seizures	➢ With or without status epilepticus, occurring within one week of stroke, traumatic brain injury, anoxic encephalopathy, or intracranial surgery

	➢ First identification of subdural hematoma or central nervous system infection ➢ Active phase of multiple sclerosis/autoimmune disorders
Deaths indirectly due to epilepsy	➢ Aspiration pneumonia ➢ Suicide ➢ Cardiovascular disease caused by antiepileptic drugs
Deaths due to underlying neurologic disease	➢ Brain tumor ➢ Stroke ➢ Metabolic [in which we included alcohol]*/genetic/neurodegenerative disease

Abbreviations: SUDEP = sudden unexpected death in epilepsy || *Alcohol included owing to alcohol-related structural brain changes resulting in a strong and consistent association between chronic alcohol consumption and unprovoked seizures (i.e. epilepsy) outside of withdrawal seizures (Samokhvalov et al. 2010).

2. Methods

2.1 Protocol and registration

An *a priori* study design was provided through registration of a protocol on PROSPERO (CRD42018102544 available from https://goo.gl/2UpNQM). The research questions and inclusion criteria were established before conduct of the review (Shea et al. 2007b; Shea et al. 2007a; Shea et al. 2009). The review follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) system of reporting (Moher et al. 2009). Ethical approval was not required.

2.2 Eligibility criteria

We applied the following inclusion criteria:

i. *Study design:* systematic reviews, i.e. a systematic search strategy was applied to one or more electronic databases *and* findings were summarized either narratively or in a formal meta-analysis (Clarke 2008);
ii. *Population of interest:* the reviews covered PWE who have died at any age, anywhere in the world;
iii. *Evaluation of interest:* the reviews reported rate or comparative risk, all-cause mortality, or different risk factors for mortality in PWE;
iv. *Outcomes of interest*: the reviews reported standardized mortality ratio (SMR), relative risk (RR), odds ratio (OR), hazard ratio (HR), mortality rate (MR), rate ratio, case fatality (CF), or proportionate mortality ratio (PMR).

We applied the following exclusion criteria:

i. Systematic reviews focusing only on a specific individual cause of death in PWE unless the cause of death was epilepsy-related (table 1) and the systematic review ascertained risk factors for this epilepsy-related cause of death. This exclusion meant we retained the ability to calculate the proportion of all-cause mortality attributable to epilepsy whilst not missing information on the risk factors for individual epilepsy-related causes of death (which may be reported in separate systematic reviews to those on all-cause mortality);

ii. Systematic reviews of mortality in highly selected subpopulations of PWE only (e.g. intellectual disability or those undergoing epilepsy surgery) if not consistent with exclusion i. above. This was aimed at increasing generalizability of the review findings (Nevalainen et al. 2014; Watila et al. 2018);

iii. Systematic reviews unable to capture any new primary studies/outcomes not already captured by other included systematic reviews. This would reduce the risks of reporting duplicate information.

iv. Systematic reviews focusing only on status epilepticus, febrile convulsions, or infantile spasms, as these patient cohorts do not necessarily have epilepsy.

2.3 Information sources, literature searches and study selection

MEDLINE and Embase (including Embase grey literature) were searched from their conception to 26/12/2018 (date last searched - 30/12/18) for potentially eligible systematic review articles (Moher et al. 2009). The full search strategy is detailed in appendix A. Reference lists of potentially eligible systematic reviews were also hand searched to identify any other potentially eligible systematic reviews. Two study authors (GKM and KB) independently screened titles, abstracts, or full-length articles against the inclusion/exclusion criteria and selected the eligible articles for inclusion. Any disagreements in article selection were resolved by consensus or, where necessary, adjunction by a third reviewer (RFMC). There were no language restrictions and, where necessary, translations were sought (Moher et al. 2009).

2.4 Data abstraction

Two study authors (GM and KB) independently abstracted data pertaining to study design, population demographics, and mortality rate, causes, and risk factors from included systematic review articles using a piloted data abstraction form (appendix B). Any differences in the abstracted study results between the two authors were resolved by mutual review of the relevant study article. Individual study data were sought from within the systematic reviews and their supplementary material tables, where available, and any missing data were sought from the original study publications.

2.5 Quality assessment of reviews

A MeaSurement Tool to Assess systematic Reviews (AMSTAR) (Shea et al. 2007b; Shea et al. 2007a; Shea et al. 2009) was used to assess systematic review quality. This validated tool assesses the degree to which review methods have avoided bias by evaluating them against 11 distinct criteria. Systematic reviews with an AMSTAR score of ≤3, 4–7, or 8–11 are considered low-, moderate-, or high-quality, respectively (Ryan et al. 2014). Two authors (GM and KB) independently assessed the quality of included reviews against the AMSTAR tool. Disagreements in scoring were resolved by consensus or, where necessary, adjunction by a third reviewer (RFMC).

2.6 Summary measures and Synthesis of results

Two review authors (GM and KB) used Devinsky's classification system of epilepsy-related deaths (Devinsky et al. 2016), summarized in table 1, to independently organize the causes of death identified within systematic reviews according to whether or not they were likely to be epilepsy-related. Any disagreements were resolved by consensus or, where necessary, adjunction by a third reviewer (RFMC). Meta-analysis across systematic reviews was not attempted because of the already well-described heterogeneity known amongst epilepsy mortality data (Levira et al. 2016; Shackleton et al. 2002; Watila et al. 2018), which has precluded previous attempts at meta-analysis (Levira et al. 2016; Shackleton et al. 2002; Watila et al. 2018) and resulted in cautioning against this (Keezer et al. 2015; Logroscino and Hesdorffer 2005). Therefore, we performed a narrative synthesis of review findings to present results (Clarke 2008; Corry et al. 2015; Lunny et al. 2017; Smith et al. 2011). Primary outcome was SMR, the most frequently used outcome measure across epilepsy mortality studies. Secondary outcomes were mortality rate, relative risk, hazard ratio, case fatality, odds ratio, proportionate mortality ratio, and rate ratios. These outcomes were used to summarize information in a primary analysis around the rate and comparative risks for all-cause mortality, causes of death and the proportion that are epilepsy-related, and risk-factors for all-cause and epilepsy-related mortality. A preliminary screen of the data for distribution, using histograms and Shapiro–Wilk testing, indicated that they were not normally distributed ($p < 0.05$ on Shapiro–Wilk test). Therefore, medians and ranges were reported for the primary analysis (Levira et al. 2016; Thurman et al. 2017). Subgroup analysis would be used to explore the results from any low-quality systematic reviews (AMSTAR quality assessment) (Shea et al. 2007b; Shea et al. 2007a; Shea et al. 2009) as compared to those from moderate- and high-quality systematic reviews combined. Our secondary analysis consisted of a narrative summary of systematic reviews that identified risk factors for an individual epilepsy-related cause of death. All analyses were performed and graphical images created using IBM SPSS Statistics Version 24, Armonk, NY: IBM Corp.

3. Results

The MEDLINE and Embase searches retrieved 47 and 238 records, respectively. Figure 1 summarizes how these were handled. Six systematic reviews were included in the primary analysis (Escalaya et al. 2015; Levira et al. 2016; Nevalainen et al. 2014; Shackleton et al. 2002; Thurman et al. 2017; Watila et al. 2018). These will be referred to as Watila 2018, Levira 2017, Thurman 2017, Escalaya 2015, Nevalainen 2014, and Shackleton 2002 in the remaining text. There were 192 studies reported across the six systematic reviews: 63 in Watila 2018, 18 in Levira 2017, 46 in Thurman 2017, 5 in Escalaya 2015, 37 in Nevalainen 2014, and 23 in Shackleton 2002. 142 of these studies featured in more than one systematic review (with 25 studies overlapping two systematic reviews, 20 studies overlapping three systematic reviews, and eight studies overlapping four systematic reviews). For overlapping studies, we extracted their result from a single systematic review only in order to avoid reporting the same data more than once. Therefore, excluding duplicate data, the primary analysis reports results from 103 studies (appendix D). 50 of these (49%) did not overlap across systematic reviews and therefore contribute independent data. The secondary analysis is a narrative synthesis of risk factors for epilepsy-related deaths from nine systematic reviews investigating a single epilepsy-related death in each. Seven systematic reviews assessed risk factors for SUDEP (Abdel-Mannan et al. 2018; Ali et al. 2017; Harden et al. 2017; Liebenthal et al. 2015; Monte et al. 2007; Tellez-Zenteno et al. 2005; Young et al. 2015). One assessed risk factors for drowning (Bell et al. 2008) and a related review dealt with suicide (Bell et al. 2009). A reference list of excluded records is provided in appendix C (Moher et al. 2009).

3.1 Primary analysis – systematic reviews assessing all-causes and risk factors

3.1.1 Characteristics of included systematic reviews

Table 2 summarizes the baseline characteristics of systematic reviews included in the primary analysis. Studies were largely sourced from MEDLINE, Embase, and Latin American and Caribbean Health Sciences Literature (LILACS). There were no age restrictions for the populations covered by each systematic review. All studies were observational (cohort or case-control designs). They covered both incident cases (mortality in people recruited into a study when newly diagnosed with epilepsy) and prevalent cases (mortality in people already known to have epilepsy when recruited), as well as both hospital- and community-based source populations. Watila 2018, Levira 2017 and Shackleton 2002 discovered significant levels of heterogeneity between studies. Therefore, they did not pool results into a meta-analysis, instead providing a narrative synthesis of results that included medians and ranges. Thurman 2017 also provided a narrative synthesis of results with medians and ranges. Nevalainen 2014 discovered significant

levels of heterogeneity between studies but still decided to pool results into a meta-analysis, and that approach was later criticized elsewhere by Thurman et al. (Keezer et al. 2015).

Table 2: Characteristics of included systematic reviews

Study characteristics		Watila 2018	Levira 2017	Thurman 2017	Escalaya 2015	Nevalainen 2014	Shackleton 2002
Review objectives	Identify rate of mortality in people with epilepsy	×	✓	×	✓	×	×
	Identify comparative risk of mortality in people with epilepsy	✓	✓	✓	✓	✓	✓
	Assess cause of death in people with epilepsy	✓	✓	✓	✓	×	×
	Identify risk factors for mortality in people with epilepsy	×	✓	✓	✓	✓	×
Populations covered	Low- and middle-income countries	✓	✓	×	✓	✓	✓
	High-income countries	✓	×	✓	×	✓	✓
Search strategy	MEDLINE	✓	✓	✓	✓	✓	✓
	Embase	✓	✓	✓	✓	×	×
	Ovid	×	×	✓	×	×	✓
	LILACS	×	✓	×	✓	✓	×
	Scopus	×	×	×	×	✓	×
	Web of Science	×	×	×	×	✓	×
	PsycINFO	×	×	×	×	✓	×
	Cochrane Library	×	×	×	×	✓	×
	CINAHL	×	×	×	×	✓	×
	IngentaConnect	×	×	×	×	✓	
	Cumulative Index Medicus	×	×	×	×	×	✓
	Exerpta Medica	×	×	×	×	×	✓
	Epilepsy Bibliography	×	×	×	×	×	✓
	WHO Global Health Library	×	×	×	×	✓	×
	African Index Medicus	×	×	×	×	✓	×
	IMEMR	×	×	×	×	✓	×
	IMSEAR	×	×	×	×	✓	×
	WPRIM	×	×	×	×	✓	×
	IBECS	×	×	×	×	✓	×
	SciELO	×	×	×	×	✓	×

	MedCarib	×	×	×	×	✓	×
Study design	Cohort studies	✓	✓	✓	✓	✓	✓
	Case-control studies	×	✓	✓	×	×	×
Quality assessment tools used	Watila 2018	Modified Newcastle–Ottawa scale and the ILAE standards for epidemiology					
	Levira 2017	Ranked studies either 0/5, 10, 15, or 20 out of 20 across five quality domains					
	Thurman 2017	Ranked studies 1, 2, 3, or 4 in increasing quality strength across the same five quality domains as Levira 2017					
	Escalaya 2015	Did not report a study quality assessment method					
	Nevalainen 2014	Newcastle-Ottawa Scale for quality assessment and GRADE system evaluation of strength of evidence.					
	Shackleton 2002	Did not report a study quality assessment method					

Abbreviations: LILACS - Latin American and Caribbean Health Sciences Literature; CINAHL - Cumulative Index to Nursing and Allied Health Literature; IMEMR - Index Medicus for the WHO Eastern Mediterranean Region; IMSEAR - Index Medicus for South-East Asia Region; WPRIM - Western Pacific Region Index Medicus; SciELO - Scientific Electronic Library Online; MedCarib - Caribbean Network of Health Sciences Libraries; ILAE - International League Against Epilepsy; GRADE - Grading of Recommendations Assessment, Development and Evaluation.

3.1.2 Quality of included systematic reviews

Watila 2018 and Nevalainen 2014 were high-quality, scoring 9 out of possible maximum score of 11 on the AMSTAR scale. The remaining reviews were moderate quality, scoring 7 out of 11 for both Levira 2017 and Thurman 2017, and 5 out of 11 for both Escalaya 2015 and Shackleton 2002. The few points lost were mainly for failure to mention a protocol or *a priori* published research objectives (six reviews), failure to provide a list of the excluded studies (five reviews), failure to disclose that grey/unpublished literature were sought (four reviews), and failure to assess the likelihood of publication bias (four reviews, appendix E) (Shea et al. 2007b; Shea et al. 2007a; Shea et al. 2009).

3.1.3 Overall risk of mortality

Figure 2 demonstrates a panel of box plots indicating the overall median and range of SMRs stratified according to various subgroups of interest. Figure 2A shows that mortality results were broadly similar between systematic reviews, with median SMR ranging between 2.3–3.6. This indicates that the overall mortality was similar for the two high-quality reviews (Watila 2018 and Nevalainen 2014) and the remaining moderate quality reviews. Two major study outliers identified in Nevalainen 2014 reported SMRs of 22.4 (Ackers et al. 2011) and 22.2 (Moseley et al. 2013). These studies were both in children (age < 18 years). Figure 2B indicates that whilst both children and adults were at increased risk of death compared to the general population, this risk tended to be higher for children (SMR range 3.1–22.4, median 7.5) than for adults (SMR range 1.3–8.7, median 2.6). Figure 2C shows that SMR results appeared broadly similar between community-based (median SMR 2.6) and hospital-based studies (median 3.1), with a tendency toward higher SMR results in hospital-based studies after the two pediatric community outliers were taken

into account. Figure 2D shows that SMR results appeared broadly similar between incident or prevalent epilepsy cohorts, with median SMR ranging 2.2–2.9 across these groups. Figure 2E indicates that there has been little change in the overall mortality of epilepsy since the 1950s, with median SMR remaining increased between 2.2–3.4. It also demonstrates that the number of epilepsy mortality studies conducted per decade has been steadily increasing, with only one study per decade in the 1930s–1940s, rising up to 24–28 studies per decade since the year 2000. In figure 2F, continents demonstrate three levels of increased risk, with the highest being in Africa (SMR range 2.6–7.2, median 5.4), followed by Eastern Asia and North America (median SMR range 3.6–3.7), and then Europe, South Asia, and South America (median SMR range 2.5–2.6).

Only Levira 2017 provided overall mortality as an MR. This was presented as the median MR for community-based studies with quality scores >80% (seven studies), with a rate of 19.8 deaths per 1,000 PWE per year (range 9.7–45.1), a weighted mean follow-up period of 5.8 years (range 1.5–10), and a total of 6,665 person-years observation. The median MR for community-based studies with lower quality scores was 13.1 deaths per 1,000 PWE per year (range 7.9–34.9), with a weighted mean follow-up period of 6.0 years (range 4.5–14) and total of 32,850 person-years observation. All of the hospital-based studies had quality scores <50%. Their median MR was 7.1 deaths per 1,000 PWE per year (range 1.6–25.1), with a weighted mean follow-up period of 12.4 years (range 3–30) and total of 33,990 person-years observation.

For studies not reporting SMR or MR, Watila 2018 reported an overall HR range of 1.9–11.9, and Levira 2017 reported an overall CF of 8.1% (range 3.3–31.6%) for high-quality community-based studies, and 5.4% (range 1.3–75.3%) for hospital-based studies.

3.1.4 Causes of death in people with epilepsy

Four systematic reviews investigated cause of death (Escalaya et al. 2015; Levira et al. 2016; Thurman et al. 2017; Watila et al. 2018). Between these, 20 causes of death were reported. These came from various sources (figure 3). Verbal autopsies and family reports were more common in low- and middle-income countries, whilst high-income countries tended to use death certificates and death registries.

3.1.5 Epilepsy-related mortality

The mortality likely to be related to epilepsy was largely reported using SMR, MR and PMR. Visual inspection of the SMR data revealed that PWE were at increased risk of death from all of the epilepsy-related causes, with three levels of risk (figure 4A). The highest risk was from alcohol, brain tumors, fires, drowning, and falls, where median

SMR ranged between 5.2–24.6. This was followed by risk from pneumonia, suicide, and injuries, where median SMR ranged between 3.2–3.9. Finally, cerebrovascular disease and transport accidents had a median SMR around 2.5. SUDEP and status epilepticus were not reported using SMR.

For PMR (figure 4B), visual inspection of the data also revealed three main groups of risk. The highest risk group died of causes that are likely to be indirectly due to epilepsy or due to underlying neurological disease (Devinsky et al. 2016), i.e. brain tumor, pneumonia and cerebrovascular disease, where PMR ranged between 19.7–50.0%. This was followed by status epilepticus, SUDEP, and drowning, where PMR ranged between 12.1–14.8%. The final group, each with PMR less than 10%, were suicide, burns, transport accidents, and falls.

SUDEP and status epilepticus were also investigated using MR (figure 4C). Rates tended to be higher for SUDEP (range 0.20–6.30, median 1.32 per 1,000 PWE per year) than for status epilepticus (range 0.09–0.97, median 0.32 per 1,000 PWE per year). More studies investigated SUDEP (32 studies) than any other cause of death.

One study from Thurman 2017 reported epilepsy-related causes of death using OR. They identified highest risk from falls, drowning, and suicide, with an OR range between 3.7–8.5 (Fazel et al. 2013). Lowest risk was from transport accidents and assault, ranging between 1.4–2.8 (Fazel et al. 2013). In Watila 2018, an MR rate ratio of 15.96 was reported for suicide (Christensen et al. 2015), alongside an HR of 2.54 (Nevalainen et al. 2013). HR was also 3.05 for accidents (Nevalainen et al. 2013), and 1.0–3.4 for alcohol (Nevalainen et al. 2012; Nevalainen et al. 2013).

3.1.6 Mortality unrelated to epilepsy

Mortality likely to be unrelated to epilepsy was largely reported using SMR and PMR. For SMR (figure 5A), visual inspection of the data revealed two broad categories of risk. The highest category was risk of death from congenital anomalies or toxic effects (carbon monoxide and pesticides), with median SMR ranging between 9.2–12.1. The lower category was risk of death from 'other' diseases (not otherwise specified), neoplasia, digestive diseases, and cardiovascular disease, with median SMR ranging between 1.5–2.0.

PMR was high across all of the causes (other diseases, unknown causes, and sepsis), ranging between 15.2–33.5% (figure 5B).

3.1.7 Comparison of epilepsy-related and unrelated causes

Figure 5C combines the results of studies showing epilepsy-related and unrelated causes using the primary outcome, SMR (23 studies). SMR results tended to be higher for epilepsy-related causes (median 3.8, range 0.0–82.4), than for

unrelated causes (median 1.7, range 0.7–17.6), suggesting more PWE are likely to die prematurely from epilepsy-related causes of death. Epilepsy-related causes constituted 60% (12 out of 20) of the reasons PWE died.

3.1.8 Risk factors for all-cause mortality in people with epilepsy

Risk factors were reported using SMR, PMR, MR, RR, and HR. Inspection of SMR results reveals that the highest risk to a person with epilepsy appears to come from their comorbidities, type of epilepsy, treatment adherence, and their age at onset of epilepsy (figure 6). Equally important are a patient's age, and how long they have had epilepsy (figure 7, A–D).

In comorbidities (figure 6), brain tumors, intellectual disabilities/cerebral palsy, and encephalopathies conferred particularly high risk, with an SMR ranging between 24.0–41.5. The types of epilepsy with a particularly high risk were congenital or developmental epilepsies (18.6-times increased median risk), and symptomatic epilepsies (3.3-times increased median risk). SMR was high for both poor and good treatment adherence groups, 8.0 and 7.4, respectively. These were self-reported outcomes, investigated by one study only. Whilst both childhood-onset and adult-onset epilepsies were associated with increased risk of death compared to the general population, this risk tended to be higher for the childhood-onset epilepsies (SMR range 5.7–46.4, median 7.3) than for adult-onset epilepsies (SMR range 1.3–10.7, median 6.0). The type of seizures, frequency of seizures, and gender appeared to be all around the same level of increased risk as each other. Within those groups, the peak SMR record came from generalized seizures (2.7-times increased median risk), increased seizure frequency (2.4-times increased median risk), and being male (2.3-times increased median risk).

In terms of age, children (<18 years old) and young adults (≤ 50 years) were at particularly high risk of death (figure 7, A–C), with SMRs ranging between 3.5–14.4. SMRs decreased with age. Risk also appeared high in the first four years after diagnosis (8.6-times increased risk), and 10–14 years after diagnosis (23.8-times increased risk) (figure 7D).

PMRs, MRs, HRs and RRs showed a broadly similar picture to SMR in terms of risk (figure 7, E–H), with the greatest risk signals associated with symptomatic epilepsy (figure 7E, 6G), male gender (figure 7E), comorbidities (particularly encephalopathies, intellectual disability/cerebral palsy, and brain tumors, figure 7F), and the period soon after epilepsy diagnosis (figure 7H). PMR results suggested increased risk associated with focal seizures compared to generalized seizures (figure 7E), in paradox to the findings of studies that used SMR to assess type of seizures as a risk factor (figure 6). Levira 2017 reported a study that investigated treatment adherence by monitoring medication

possession, demonstrating increased risk of death in association with nonadherence to antiepileptic drugs (AEDs) compared to adherence (rate ratio 3.37, 95% CI 1.84–6.16) (Ngugi et al. 2014).

3.1.9 Risk factors for epilepsy-related mortality

From the four systematic reviews that investigated cause of death (Escalaya et al. 2015; Levira et al. 2016; Thurman et al. 2017; Watila et al. 2018), risk factors were reported for all-cause mortality. The reviews made no attempts to further subclassify risk factors according to whether or not they were in association with epilepsy-related versus unrelated causes of death.

3.2 Secondary analysis – systematic reviews of risk factors for individual epilepsy-related causes of death

The epilepsy-related causes of death for which there were systematic reviews of their risk factors were SUDEP, drowning, and suicide.

3.2.1 SUDEP

SUDEP was the epilepsy-related cause of death with the greatest number of systematic reviews of its risk factors. This was done across seven systematic reviews. Four of these assessed multiple risk factors for SUDEP. The earliest, Téllez-Zenteno 2005 (Tellez-Zenteno et al. 2005), was of moderate quality (appendix E) and included 36 studies (cohort and case-control studies) of SUDEP at all ages. They assessed for the positive presence of a risk factor amongst SUDEP cases within included studies. The most consistent risk factors were seizures preceding death (with most patients found dead in bed), and subtherapeutic AED levels (80% of studies). Other positive risk factors were youth (defined as age 15–30 years) in 50% of studies, high seizure frequency (>15 per month) in 60%, a high number of AEDs (>2) in 50%, and a long duration of epilepsy (>15 years) in 50% of studies. Monté 2007 (Monte et al. 2007) was also of moderate quality (appendix E). The authors recognized conflicting data on SUDEP risk factors following Téllez-Zenteno 2005 and sought to address this using risk factor total studies ratios (RFT), which were values based on the results in studies analyzing the risk factor corrected for the total number of included SUDEP cases in the different studies. RFT scores of ≥1.0, ≥0.5, and <0.5 were considered to indicate a strong, weak, and absent risk factor for SUDEP, respectively. The strong risk factors were young age (<45 years), early onset of seizures (<45 years at diagnosis), the presence of generalized tonic-clonic seizures (GTCS), male sex and being in bed. Harden 2017 (Harden et al. 2017) then developed a clinical practice guideline summary for SUDEP. In this moderate-quality systematic review (appendix E), they looked at SUDEP in all ages from 70 studies (clinical trials and observational studies) and identified GTCS as the greatest risk factor (OR 10, 95% CI 14–17). Others were increased frequency of

GTCS: OR 15.46 (95% CI 9.92–24.10) for >3 GTCS per year and OR 5.07 (95% CI 95% 2.94–8.76) for 1–2 GTCS per year, not adding in another AED to refractory patients (OR 6, 95% CI 2–20), and not being seizure-free for 1–5 years (OR 4.7, 95% CI 1.4–16). Protective factors were nocturnal supervision (OR 0.4, 95% CI 0.2–0.8), and use of a nocturnal listening device (OR 0.1, 95% CI 0–0.3). Abdel-Mannan 2018 (Abdel-Mannan et al. 2018) then recognized that there had not been a focus on children in SUDEP systematic reviews. In this high-quality systematic review (appendix E), they identified 108 pediatric cases (age ≤18 years) of SUDEP from 22 studies including cohorts, case-controls, case series, and case reports. Increased SUDEP was associated with GTCS (affecting 88% of participants), chronic brain lesions (affecting 61%), male sex (51% males), and cognitive or developmental delay (affecting 45%).

Other SUDEP systematic reviews focused on an individual risk factor for SUDEP. Young 2015 (Young et al. 2015), a low-quality systematic review (appendix E), looked at intellectual disability as a risk factor. From 23 studies assessing this risk factor, 60% (14 studies) found it was positively associated with SUDEP. In a moderate-quality systematic review (appendix E), Liebenthal 2015 (Liebenthal et al. 2015) investigated the association between a prone body position and SUDEP in all ages from 253 cases in 25 studies (case reports and case series). 73.3% (95% CI 65.7–80.9%) died in a prone position, compared to 26.7% (95% CI 16.3–37.1%) dying in a nonprone position ($p < 0.001$). A prone position was found in 85.7% (95% CI 74.6–93.3%) of those aged ≤40 years compared to 60% (95% CI 5 38.7%, 78.9%) of patients >40 years (OR 3.9, 95% CI 1.4–11.4%). In their moderate-quality systematic review (appendix E), Ali 2017 (Ali et al. 2017) investigated the associated of sleep with SUDEP, identifying 880 cases from 67 studies (a mixture of case reports and case series in participants of all ages). SUDEP was significantly associated with sleep compared to wakefulness ($p < 0.001$), and patients ≤40 years were more likely to have SUDEP in sleep than those older (OR 2.0, 95% CI 1.0–3.8). 87.6% (95% CI 81.1–94.2%) of those experiencing SUDEP in sleep were in a prone position compared to 52.9% (95% CI 4.7–81.1%) during wakefulness. Patients with night-time seizures were 6.3 times more likely to have SUDEP when in a prone position than those with diurnal seizures (OR 6.3, 95% CI 2.0–19.5).

3.2.2 Drowning

In their moderate-quality systematic review, Bell 2008 (Bell et al. 2008) assessed risk factors for drowning in PWE of all ages, identifying 88 drowning deaths from 51 cohorts. Drowning was more closely associated with an established diagnosis of epilepsy (prevalent epilepsy SMR 18.0, 95% CI 12.9–24.4) than newly diagnosed epilepsy (incident epilepsy SMR 5.4, 95% CI 1.5–13.9). Other positive risk factors were learning disability (SMR 25.7, 95%

CI 16.6–38.0), institutional care (SMR 96.9, 95% CI 26.4–248), and temporal lobe excision (SMR 41.1, 95% CI 11.2–105). Risks of drowning were highest in Africa.

3.2.3 Suicide

In another moderate-quality systematic review, Bell 2009 (Bell et al. 2009) assessed risk factors for suicide in PWE of all ages, identifying 190 suicides from 76 cohorts. Suicide was most closely associated with temporal lobe excision (SMR 13.9, 95% CI 8.93–20.74), temporal lobe epilepsy (SMR 6.57, 95% CI 1.79–16.8), epilepsy surgery (SMR 6.37, 95% CI 3.06–11.72), and an established diagnosis of epilepsy (prevalent epilepsy SMR 4.81, 95% CI 3.08–7.16). Developmental disability was associated with lower suicide risks (SMR 0.34, 95% CI 0.07–0.99).

4. Discussion

4.1 Areas of novelty

There are three main areas of novelty within the current systematic review. First, systematically reviewing the systematic reviews of mortality in PWE has allowed us to draw conclusions using a primary analysis from a much larger sample of evidence than any previous systematic review of this topic, since we have captured 103 studies (40 more studies than was captured by the next largest review (Watila et al. 2018)). This is important because as a method, systematic review should aim to evaluate an entire body of evidence surrounding a topic (Higgins JPT and Green S 2011). Inspection of table 2 reveals that some of the likely reasons for lack of overlap in included studies from the systematic reviews are variation in primary outcomes (Nevalainen 2014 and Shackleton 2002, for example, did not assess causes of death), variation in the number of electronic databases searched (Watila 2018, Levira 2017, Thurman 2017 and Escalaya 2015 searched 2–3 whilst Nevalainen 2014 searched 16), and variation in included study designs (Levira 2017 and Thurman 2017 included both cohort and case-control studies, whilst the remainder included only cohort studies). The second area of novelty is that we have applied a recently published classification system (Devinsky et al. 2016) to allow us to quantify epilepsy-related and unrelated deaths. This has not been done before, and it has allowed us to include within the epilepsy-related dataset, causes not originally classed as epilepsy-related within the included systematic reviews, e.g. alcohol, pneumonia, and suicide. Third, our secondary analysis gives an overview of the risk factors for epilepsy-related mortality, identifying that these have failed to be captured by systematic reviews of all-cause mortality in which epilepsy-related causes of death were included. Finally, we have provided the first independent quality assessment of the epilepsy mortality systematic reviews.

Our most novel findings beyond those identified in the original reviews are that:

1) Despite presumed advances in epilepsy diagnostics and therapeutics, overall mortality in PWE has remained high and virtually unchanged in the decades since 1950. The reasons for this are unclear and this requires further investigation. One possible explanation is increased reporting of epilepsy on death certificates over the last 10–20 years due to improved physician education occurring at the same time as improvements in epilepsy care. The former would act to increase reported rates whilst the latter would act to reduce actual rates, resulting in a net lack of change in final mortality rate figures (Neligan et al. 2010);
2) Overall mortality is highest in Africa and there are also no studies in Australasia, the Middle East, South East Asia, and Russia. Some of the possible reasons for higher mortality in Africa include that the condition remains stigmatized widely there (Belhocine M et al. 2004), there are limited health personnel and facilities for diagnosis and treatment, and there are major treatment gaps, with as high as 80–85% of PWE not diagnosed or treated (Donner et al. 2001);
3) Epilepsy-related mortality predominates causes of death, with an SMR of more than twice that of unrelated causes and accounting for 60% of the reasons PWE died;
4) Whilst SUDEP contributes to a high proportion of epilepsy-related causes of death, other epilepsy-related causes are likely to be similarly lethal including alcohol, drowning, pneumonia, and suicide (these may be preventable (Devinsky et al. 2016; Hanna et al. 2002; Neligan and Sander 2011));
5) Risk factors for epilepsy-related deaths specifically, as a group, remain uncharacterized. However, risk factors for individual epilepsy-related deaths have been looked at largely for SUDEP, but also for drowning and suicide. For SUDEP, youth (age under 30-45 years) and the presence of GTCS appear to be the risk factors most commonly reported as significant across systematic reviews of multiple SUDEP risk factors, and reviews of individual SUDEP risk factors add further information that not only is SUDEP risk greatest in the prone position, but that this is more so in youth. Between them, the systematic reviews also identify other pertinent SUDEP risk factors as nocturnal seizures or sleep (particularly in the prone position), increased seizure frequency (particularly generalized seizures) or lack of seizure freedom, intellectual disability/developmental delay, undertreatment (subtherapeutic AED levels or incomplete treatment of refractory epilepsy), and male sex. Nocturnal supervision and listening devices are suggested to be protective, although this is only mentioned one systematic review. SUDEP risk factors are similar for children and adults although there are additional reports of chronic brain lesions and developmental delay as significant risk factors in children. Drowning appears to be most closely associated with chronic epilepsy, learning difficulty, temporal lobe surgery, and institutional care. The latter is

surprising, given that institutional care is assumed to involve greater supervision for patients. Although Africa conferred the highest risks of drowning for PWE, the World Health Organization reports that drowning rates in the general population worldwide are highest in Africa anyway (World Health Oraganization 2018). Suicide appears to also be associated with temporal lobe epilepsy pathology/intervention and chronic epilepsy, whilst developmental delay is protective for this. The reasons for a link to temporal lobe pathology remain unclear (Bell et al. 2009). Similarly, it is unlikely that lower suicide risk is due to greater supervision in those with developmental delay because risk of drowning remains high in institutional care, where many of such patients are.

4.2 Implications and areas for future research

The primary analysis reveals that the overall risks of mortality were consistently high across systematic reviews, compared to the general population, in line with the two-to-threefold increase frequently quoted in the literature (Neligan A and Bell GS 2009). This result was unaffected by systematic review quality. The consistent finding that children and young adults had the highest risk of death may be explained by a high incidence of congenital or symptomatic epilepsies in children (Levira et al. 2016), which we found to be pertinent risk factors for premature death. It may also be explained by comparatively lower mortality rates in the general population at a younger age (Levira et al. 2016). This highlights one of the limitations of comparative measures, such as SMR. They can mask absolute increases in the rate of mortality of a study population if equal to the general population's (Thurman et al. 2017), even if the causes of death in the study and general population differ. Thus, we propose that more work needs to be done to ascertain and report on absolute mortality rates, rather than studies and systematic reviews only reporting comparative measures. Absolute MR was reported only in one systematic review, which focused on data from low- and middle-income countries alone (Levira et al. 2016). The absolute MR burden for PWE in high-income countries remains to be clarified.

Overall mortality did not appear different between hospital- and community-based studies. This was likely to be because by excluding studies of highly selected subpopulations (such as those consisting of only surgical patients or only patients with intellectual disability), the hospital sample became more equally representative of the community sample (Nevalainen et al. 2014). This helps highlight how epilepsy still remains a major cause of death even in the community. Therefore, it will remain important for future studies investigating mortality in PWE to include both hospital and community populations.

This is the first systematic review to make an attempt to quantify epilepsy-related mortality using a formal classification system (Devinsky et al. 2016). Whilst researchers can never be absolutely certain that a death was epilepsy-related, even in the event of a post-mortem (Devinsky et al. 2016), the classification system helps us to functionally categorize deaths into those that are most likely to be epilepsy-related. Given the variation in defining epilepsy-related mortality in literature thus far (Devinsky et al. 2016), our use of the classification system in this manner, if developed and continued, should help standardize case ascertainment for epilepsy-related deaths within future primary studies and systematic reviews. One of the rationales for a need for greater consistency and quantification of epilepsy-related mortality, specifically, is that it is the epilepsy-related proportion of deaths (rather than the unrelated deaths) that are felt to most likely be preventable (Devinsky et al. 2016; Hanna et al. 2002; Neligan and Sander 2011).

The main epilepsy-related causes of death we identified were in relation to alcohol, brain tumors, SUDEP, accidents (fires, drowning, falls), pneumonia, and suicide. There is more literature on SUDEP than any other epilepsy-related cause of death (Devinsky et al. 2016). Whist increased attention on SUDEP is warranted, our report suggests that equal attention is needed toward other epilepsy-related causes, which may be similarly dangerous. For example, we found that whilst SUDEP contributed to 12% of deaths on PMR, drowning also contributed to 12%, and pneumonia contributed to 30%. It may be that national patient and family education programs may help prevent the risks of drowning. The increased risk of pneumonia in the epilepsy population is likely to be related to gastric aspiration during seizures (Devinsky et al. 2016). This may require better screening and early treatment for those at risk. The increased risk of suicide in also worrying and occurred in multiple older and newer studies worldwide (Chamorro-Munoz et al. 2017; Chang et al. 2012; Day et al. 2005; Ding et al. 2006; Ding et al. 2013; Granbichler et al. 2015; Mohanraj et al. 2006; Mu et al. 2011; Rafnsson et al. 2001; Shackleton et al. 1999; White et al. 1979). It may be that more needs to be done to manage mental health problems in PWE. We know that mood disorders represent a frequent psychiatric comorbidity in PWE, but they often remain unrecognized and untreated (Mula and Schmitz 2009). The potential association of alcohol and increased mortality requires further investigation given that this cause had the highest SMR of all epilepsy-related causes but was reported only in one study. We included alcohol in the epilepsy-related cause of death group because beyond withdrawal seizures, there is a strong and consistent association between alcohol consumption and unprovoked seizures (i.e. epilepsy), which demonstrates a dose-response relationship between the amount of alcohol consumed daily and the probability of onset of epilepsy (Samokhvalov et al. 2010).

The risk factors most strongly associated with increased all-cause mortality were comorbid diseases, particularly those affecting the brain (tumors, intellectual disability or cerebral palsy, and encephalopathies), congenital or symptomatic epilepsies, poor adherence to treatment (although limited number of studies to confirm this), young age or childhood-onset of epilepsy, the period soon after epilepsy diagnosis, and male sex. There were similarities between these and risk factors for SUDEP reported in the secondary analysis, suggesting a degree of overlap between risk factors for SUDEP and risk factors for all-cause mortality in PWE. This indicates that perhaps risk prevention strategies for SUDEP might also reduce all-cause mortality. Further work is still needed to investigate risk factors for other epilepsy-related causes beyond SUDEP, which has received the greatest literary attention, given that the other epilepsy-related deaths are also common. Only downing and suicide have been reviewed in terms of risk factor profiles. Evaluating the risk factors for epilepsy-related death together as a group would allow for the development of a risk-index scoring tool to identify PWE at high risk of epilepsy-related death (Devinsky et al. 2016) in a similar fashion to how the SUDEP and Seizure Safety Checklist identifies PWE at high risk of SUDEP (SUDEP Action 2017).

4.3 Limitations

There are several limitations to the current systematic review. Firstly, although the Devinsky classification system is set up to identify epilepsy-related deaths in PWE, it is not a perfect system and will likely need streamlining in future. For example, it may be argued that deaths due to acute symptomatic seizures should be removed as a category, as some of these patients may not go on to develop epilepsy. We did not remove this category as ours is the first review to use the original classification system, therefore it paves the way for literary debate on which categories should now be amended/removed going forward. Related to this, some proposed epilepsy-related causes may not reflect the possibility of an epilepsy-independent mechanism of death. For example, PWE may die naturally from their brain tumor, stroke, and even from a drowning, traffic accident, or fall unrelated to their epilepsy. Therefore, the classification system should remain viewed as one in which the weight of probability is that these are likely to be epilepsy-related deaths in PWE but that this is not always certain. However, the clinical importance of such a classification system remains clear. In the instances where these deaths are indeed epilepsy-related (and many are), then these should have been preventable (Devinsky et al. 2016; Hanna et al. 2002; Neligan and Sander 2011). Therefore, the classification system remains a useful tool to help clinicians and researchers start to capture and highlight information on other potential epilepsy-related deaths beyond SUDEP. A second limitation is that we were unable to address the problem of confounding. There may have been several significant confounders between

systematic reviews, particularly between the low- or middle-income countries and the higher-income countries. Confounding is usually managed using multivariate meta-regression, but this was not possible in a narrative synthesis of findings. There would have been difficulty in dealing with confounding at source, as three of the included primary analysis systematic reviews were narrative and did not use formal techniques to handle confounding (Escalaya et al. 2015; Levira et al. 2016; Thurman et al. 2017). This highlights the difficulties other authors have identified in trying to summarize the epilepsy mortality data uniformly (Logroscino and Hesdorffer 2005). Related to this, the reviews highlighted significant heterogeneity between studies, precluding valid use of meta-analysis to provide summary estimates (Keezer et al. 2015). Differences in source population and case selection are the most likely explanations for the heterogeneity (Shackleton et al. 2002). There are limitations in the utility of SMR, which assesses mortality within a study population compared to a general population stratified by age and sex. Different studies will use different age bands to stratify, and there may be differing baseline mortality rates between the different general populations used by studies. This means that any comparison of SMRs between studies should be made and interpreted with caution. This is another reason often cited for not performing meta-analysis across studies that have used SMR (Logroscino and Hesdorffer 2005). Epilepsy mortality data is limited in this way for all systematic reviews of this subject, as most studies have reported SMRs alone. We were also unable to assess the risk of publication bias. Finally, we have presented causes of death as though they were definitive. However, we note that ascertaining cause of death accurately can be challenging (Devinsky et al. 2016), especially when it comes to identifying SUDEP, where post-mortem is required. None of the studies in low- and middle-income countries used post-mortem, relying instead on verbal autopsies, which can be inaccurate (Levira et al. 2016). Furthermore, only seven of the studies in high-income countries used post-mortem. Once again, epilepsy mortality data is limited in this way for all systematic reviews of this subject, as the heterogeneity in how epilepsy mortality studies have been conducted worldwide remains. Even within the systematic review in which analysis was limited to studies from low- and middle-income countries alone (Levira et al. 2016) and in the review in which analysis was limited to those from high-income countries (Thurman et al. 2017), heterogeneity remained present. Future studies should aim to combine information from several sources, such as death certificates, information from medical records, interview with witnesses and responsible physicians, and post-mortem results. Furthermore, consensus should be reached on how such studies should be conducted in future in order to help reduce heterogeneity.

Conclusions

Despite the limitations, several implications of this review are clear. There are high-quality systematic reviews of mortality in PWE, covering the majority of the globe. However, when looked at alone, each review has been unable to identify all of the available studies. When the results of the systematic reviews are combined, they indicate that despite advances in diagnostics and therapeutics over time, mortality has remained high for PWE compared to the general population, particularly in children and young adults. Future studies should aim to ascertain not only these comparative mortality outcomes, but also the absolute mortality rates, particularly in high-income countries. Our review also indicates that there is an increased burden of epilepsy-related deaths. These present in several potentially preventable manners, so future studies and reviews of mortality in PWE would benefit from stratifying results into epilepsy-related and unrelated deaths. Risk factors for all-cause mortality and SUDEP are similar, and further work is required to investigate the risk factor profile of other epilepsy-related causes of death.

Acknowledgements

We also thank Jacqueline Stephen from The University of Edinburgh for providing statistical support.

Declarations of interest: *none*

Funding

This work was supported charitably by Epilepsy Research UK (R44007), the Juliet Bergqvist Memorial Fund, and Epilepsy Action.

Ethics approval, informed consent, trial registration: not required

5. References

Abdel-Mannan, O., et al. (2018), 'A systematic review of sudden unexpected death in epilepsy (SUDEP) in childhood', *Epilepsy Behav*, 90, 99-106.

Ackers, R., et al. (2011), 'Mortality rates and causes of death in children with epilepsy prescribed antiepileptic drugs: a retrospective cohort study using the UK General Practice Research Database', *Drug Saf*, 34 (5), 403-13.

Ali, A., et al. (2017), 'Association of sleep with sudden unexpected death in epilepsy', *Epilepsy Behav*, 76, 1-6.

Belhocine M, de Boer HM, and Mandlhate C (2004), 'Epilepsy in the WHO African Region: Bridging the Gap ', *The Global Campaign Against Epilepsy "Out of the Shadows"*. <https://www.who.int/mental_health/management/epilepsy_in_African-region.pdf>, accessed 04/07/2019.

Bell, G. S., et al. (2008), 'Drowning in people with epilepsy - How great is the risk?', *Neurology*, 71 (8), 578-82.

--- (2009), 'Suicide in people with epilepsy: how great is the risk?', *Epilepsia*, 50 (8), 1933-42.

Chamorro-Munoz, M. I., et al. (2017), 'Epidemiological study of mortality in epilepsy in a Spanish population', *Seizure*, 46, 19-23.

Chang, Y. H., et al. (2012), 'Risk of mortality among patients with epilepsy in southern Taiwan', *Seizure-European Journal of Epilepsy*, 21 (4), 254-59.

Christensen, J., et al. (2015), 'Long-term mortality in children and young adults with epilepsy--A population-based cohort study', *Epilepsy Res*, 114, 81-8.

Clarke, M. (2008), 'Systematic review of reviews of risk factors for intracranial aneurysms', *Neuroradiology*, 50 (8), 653-64.

Corry, M., et al. (2015), 'A systematic review of systematic reviews on interventions for caregivers of people with chronic conditions', *J Adv Nurs*, 71 (4), 718-34.

Day, S. M., et al. (2005), 'Causes of death in remote symptomatic epilepsy', *Neurology*, 65 (2), 216-22.

Devinsky, O., et al. (2016), 'Recognizing and preventing epilepsy-related mortality: A call for action', *Neurology*, 86 (8), 779-86.

Ding, D., et al. (2006), 'Premature mortality in people with epilepsy in rural China: a prospective study', *Lancet Neurol*, 5 (10), 823-7.

Ding, D., et al. (2013), 'Premature mortality risk in people with convulsive epilepsy: long follow-up of a cohort in rural China', *Epilepsia*, 54 (3), 512-7.

Donner, E. J., Smith, C. R., and Snead, O. C., 3rd (2001), 'Sudden unexplained death in children with epilepsy', *Neurology*, 57 (3), 430-4.

Escalaya, A. L., et al. (2015), 'Epilepsy and mortality in Latin America', *Seizure*, 25, 99-103.

Fazel, S., et al. (2013), 'Premature mortality in epilepsy and the role of psychiatric comorbidity: a total population study', *Lancet*, 382 (9905), 1646-54.

Granbichler, C. A., et al. (2015), 'Cause-specific mortality in adult epilepsy patients from Tyrol, Austria: hospital-based study', *J Neurol*, 262 (1), 126-33.

Hanna, N J., et al. (2002), 'The National Sentinel Clinical Audit of Epilepsy-Related Death: Epilepsy – death in the shadows', *The Stationery Office*.

Harden, C., et al. (2017), 'Practice guideline summary: Sudden unexpected death in epilepsy incidence rates and risk factors: Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology and the American Epilepsy Society', *Neurology*, 88 (17), 1674-80.

Higgins JPT and Green S (2011), *Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0*

Keezer, M. R., Bell, G. S., and Sander, J. W. (2015), 'Epilepsy-related clinical characteristics and mortality: a systematic review and meta-analysis', *Neurology*, 84 (17), 1823.

Levira, F., et al. (2016), 'Premature mortality of epilepsy in low- and middle-income countries: A systematic review from the Mortality Task Force of the International League Against Epilepsy', *Epilepsia*, 1-11.

Liebenthal, J. A., et al. (2015), 'Association of prone position with sudden unexpected death in epilepsy', *Neurology*, 84 (7), 703-09.

Logroscino, G. and Hesdorffer, D. C. (2005), 'Methodologic issues in studies of mortality following epilepsy: measures, types of studies, sources of cases, cohort effects, and competing risks', *Epilepsia*, 46 Suppl 11, 3-7.

Lunny, C., et al. (2017), 'Toward a comprehensive evidence map of overview of systematic review methods: paper 1-purpose, eligibility, search and data extraction', *Syst Rev*, 6 (1), 231.

Mbizvo, G. K., et al. (2012), 'Levetiracetam add-on for drug-resistant focal epilepsy: an updated Cochrane Review', *Cochrane Database Syst Rev*, 9, CD001901.

Mohanraj, R., et al. (2006), 'Mortality in adults with newly diagnosed and chronic epilepsy: a retrospective comparative study', *Lancet Neurol*, 5 (6), 481-7.

Moher, D., et al. (2009), 'Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement', *BMJ*, 339, b2535.

Monte, C. P., et al. (2007), 'Sudden unexpected death in epilepsy patients: Risk factors. A systematic review', *Seizure*, 16 (1), 1-7.

Moseley, B. D., et al. (2013), 'Early onset epilepsy is associated with increased mortality: a population-based study', *Epilepsy Res*, 105 (3), 410-4.

Mu, J., et al. (2011), 'Causes of death among people with convulsive epilepsy in rural West China: a prospective study', *Neurology*, 77 (2), 132-7.

Mula, M. and Schmitz, B. (2009), 'Depression in epilepsy: mechanisms and therapeutic approach', *Ther Adv Neurol Disord*, 2 (5), 337-44.

Neligan A and Bell GS (2009), 'The mortality of epilepsy', in Sander JW, Rugg-Gunn FJ, and Smalls JE (eds.), *Epilepsy 2009: From Benchside to Bedside - a Practical Guide to Epilepsy* (12th edn.; Chalfont St Peter: National Society for Epilepsy), pp 347-51.

Neligan, A. and Sander, J. W. (2011), 'Premature mortality in epilepsy: is it preventable?', *Expert Review of Neurotherapeutics*, 11 (6), 767-70.

Neligan, A., et al. (2010), 'Temporal trends in the mortality of people with epilepsy: a review', *Epilepsia*, 51 (11), 2241-6.

Nevalainen, O., et al. (2012), 'Mortality by clinical characteristics in a tertiary care cohort of adult patients with chronic epilepsy', *Epilepsia,* 53 (12), e212-4.

Nevalainen, O., et al. (2013), 'Long-term mortality risk by cause of death in newly diagnosed patients with epilepsy in Finland: a nationwide register-based study', *Eur J Epidemiol,* 28 (12), 981-90.

Nevalainen, O., et al. (2014), 'Epilepsy-related clinical characteristics and mortality: a systematic review and meta-analysis', *Neurology,* 83 (21), 1968-77.

Ngugi, A. K., et al. (2014), 'Premature mortality in active convulsive epilepsy in rural Kenya: causes and associated factors', *Neurology,* 82 (7), 582-9.

Rafnsson, V., et al. (2001), 'Cause-specific mortality in adults with unprovoked seizures. A population-based incidence cohort study', *Neuroepidemiology,* 20 (4), 232-6.

Ryan, R., et al. (2014), 'Interventions to improve safe and effective medicines use by consumers: an overview of systematic reviews', *Cochrane Database of Systematic Reviews,* (4).

Samokhvalov, A. V., et al. (2010), 'Alcohol consumption, unprovoked seizures, and epilepsy: a systematic review and meta-analysis', *Epilepsia,* 51 (7), 1177-84.

Shackleton, D. P., et al. (1999), 'Mortality in patients with epilepsy: 40 years of follow up in a Dutch cohort study', *J Neurol Neurosurg Psychiatry,* 66 (5), 636-40.

Shackleton, D. P., et al. (2002), 'Survival of patients with epilepsy: an estimate of the mortality risk', *Epilepsia,* 43 (4), 445-50.

Shea, B. J., et al. (2009), 'AMSTAR is a reliable and valid measurement tool to assess the methodological quality of systematic reviews', *J Clin Epidemiol,* 62 (10), 1013-20.

Shea, B. J., et al. (2007a), 'External validation of a measurement tool to assess systematic reviews (AMSTAR)', *PLoS One,* 2 (12), e1350.

Shea, B. J., et al. (2007b), 'Development of AMSTAR: a measurement tool to assess the methodological quality of systematic reviews', *BMC Med Res Methodol,* 7, 10.

Smith, V., et al. (2011), 'Methodology in conducting a systematic review of systematic reviews of healthcare interventions', *BMC Med Res Methodol,* 11 (1), 15.

SUDEP Action 'SUDEP and Seizure Safety Checklist', <https://sudep.org/checklist>, accessed 07 November 2018.

Tellez-Zenteno, J. F., Ronquillo, L. H., and Wiebe, S. (2005), 'Sudden unexpected death in epilepsy: evidence-based analysis of incidence and risk factors', *Epilepsy Res,* 65 (1-2), 101-15.

Thurman, D. J., et al. (2017), 'The burden of premature mortality of epilepsy in high-income countries: A systematic review from the Mortality Task Force of the International League Against Epilepsy', *Epilepsia,* 58 (1), 17-26.

Watila, M. M., et al. (2018), 'Overall and cause-specific premature mortality in epilepsy: A systematic review', *Epilepsy Behav*.

White, S. J., McLean, A. E., and Howland, C. (1979), 'Anticonvulsant drugs and cancer. A cohort study in patients with severe epilepsy', *Lancet*, 2 (8140), 458-61.

World Health Oraganization (2018), 'Drowning', *Fact sheets*. <https://www.who.int/news-room/fact-sheets/detail/drowning>, accessed 03/07/2019.

Young, C., et al. (2015), 'Does intellectual disability increase sudden unexpected death in epilepsy (SUDEP) risk?', *Seizure-European Journal of Epilepsy*, 25, 112-16.

Figure captions

Figure 1: Title - Flow diagram of study selection process.

Legend - A reference list of excluded studies is provided in appendix C. Abbreviations: SUDEP = sudden unexpected death in epilepsy.

Figure 2: Title - Box plot panel showing overall mortality in people with epilepsy.

Legend - The box plots show the standardized mortality ratio (SMR) stratified by various groups. (A) shows SMR for the included systematic reviews in descending median order. Results from the five studies included in Escalaya 2015 (Escalaya et al. 2015) are not shown to avoid duplication with Levira 2017 (Levira et al. 2016), who reported these same studies. (B) shows SMR for studies in adults and children. (C) shows SMR for hospital and community studies. (D) shows SMR for incident and prevalent cases. (E) shows SMR over time by decade of study publication. (F) shows SMR by continent within which studies were conducted, in descending median order. The number of studies used to generate each box plot is shown in brackets on the x-axis. $^{*/O}$ = outlier studies. Abbreviations: US = United States.

Figure 3: Title – Pie charts showing sources of cause of death information

Legend –Three of the systematic reviews assessing cause of death as an outcome are shown. Results from the five studies included in Escalaya 2015 (Escalaya et al. 2015) are not shown to avoid duplication with Levira 2017 (Levira et al. 2016), who reported these same studies.

Figure 4: Title - Panel of box plots showing epilepsy-related causes of death.

Legend - (A) standardized mortality ratio (SMR), (B) proportionate mortality ratio (PMR), (C) mortality rate (MR) for the different causes, in descending median order. The number of studies used to generate each box plot is shown in brackets on the x-axis. ^Drowning also includes submersion and suffocation; Pneumonia also includes respiratory causes; All accidents also includes injuries. */^{O} = outlier studies. Abbreviations: Cerebrovasc. dis. = cerebrovascular disease; PWE = people with epilepsy.

Figure 5: Title - Box plots panel showing mortality unrelated to epilepsy and comparison of epilepsy-related and unrelated causes.

Legend - (A) standardized mortality ratio (SMR), (B) proportionate mortality ratio (PMR), (C) epilepsy-related and unrelated causes, in descending median order. The number of studies used to generate each box plot is shown in brackets on the x-axis. ^Toxic effects includes poisoning. */^{O} = outlier studies. Abbreviations: Other dis. = other diseases; Digestive dis. = digestive diseases; Cardiovasc. dis. = cardiovascular disease.

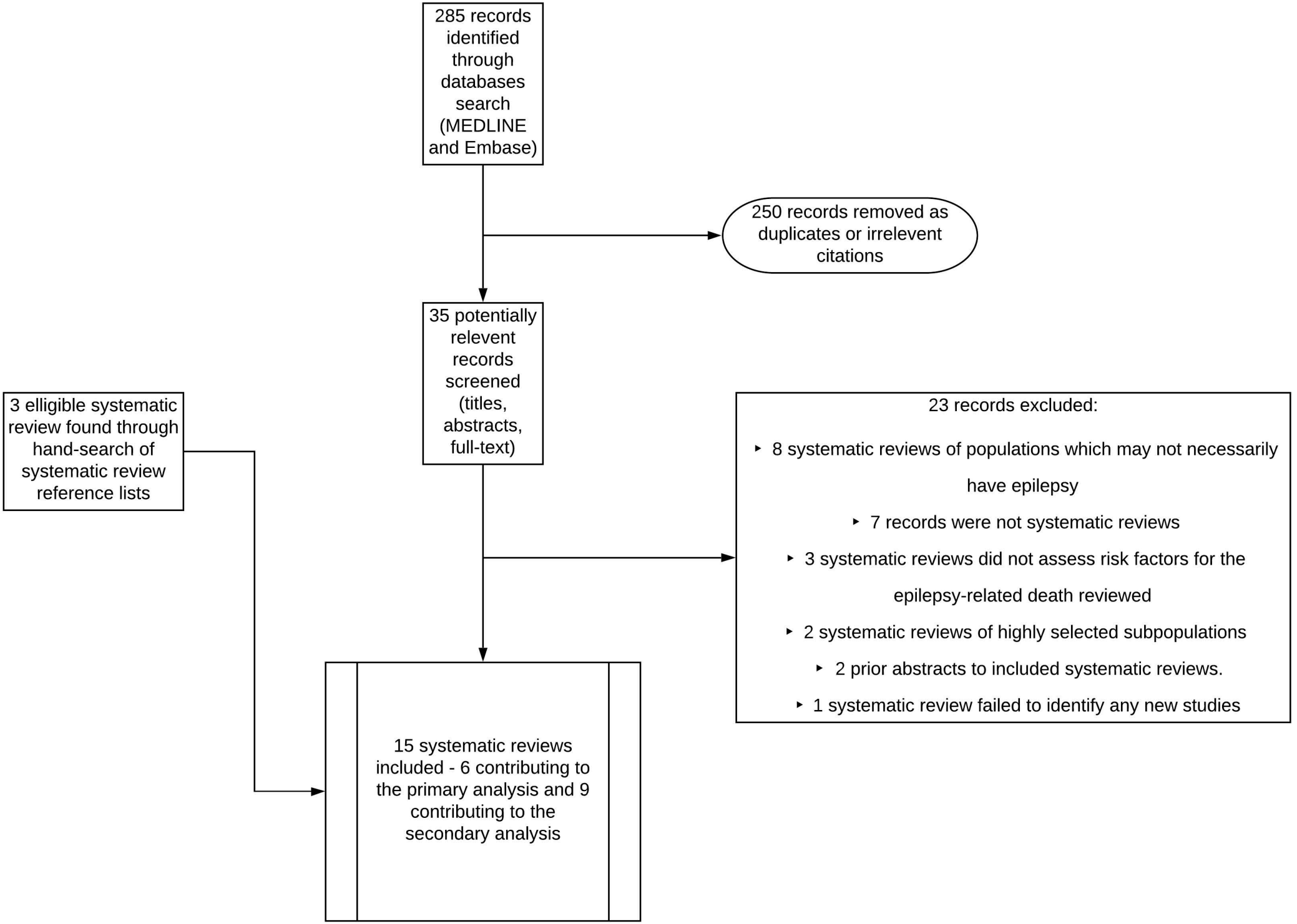
Figure 6: Title - Box plot showing mortality risk factors identified by standardized mortality ratio (SMR).

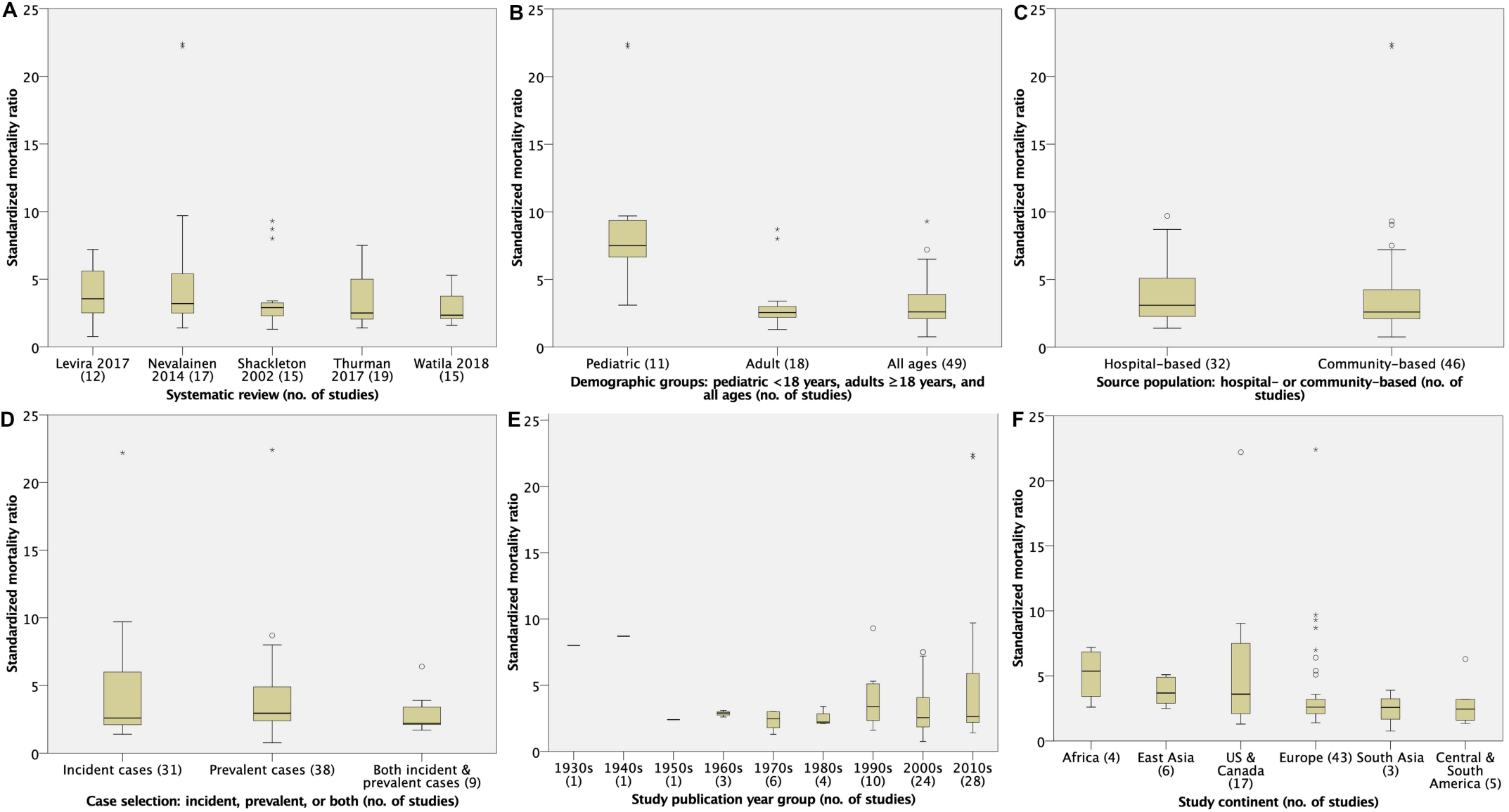
Legend – Risk factor categories are: **Comorbidities** = brain tumor, intellectual disability/cerebral palsy, encephalopathies, dementia, and cerebrovascular disease; **Epilepsy type** = congenital epilepsy, symptomatic epilepsy, undetermined epilepsy type, and cryptogenic epilepsy; **Compliance** = poor adherence and good adherence; **Onset age** = childhood-onset and adult-onset; **Seizure type** = generalized seizures and focal seizures; **Seizure frequency** = high seizure frequency and low seizure frequency; **Gender** = male and female. Plots are in descending median order within categories. The number of studies used to generate each box plot is shown in brackets on the x-axis. ^Congenital includes developmental epilepsy; Cryptogenic includes idiopathic epilepsy; Adherence was a self-reported outcome; Childhood-onset was < 18 years; Adult-onset was ≥ 18 years; High seizure frequency was >1/week or refractory; Low seizure frequency was < 1/week or seizure-free. */^{O} = outlier studies. Abbreviations: CP = cerebral palsy; Cerebrovasc. dis. = cerebrovascular disease; Other dis. = other diseases; Digestive dis. = digestive diseases; Cardiovasc. dis. = cardiovascular disease.

Figure 7: Title – Scatter and box plots showing additional mortality risk factors.

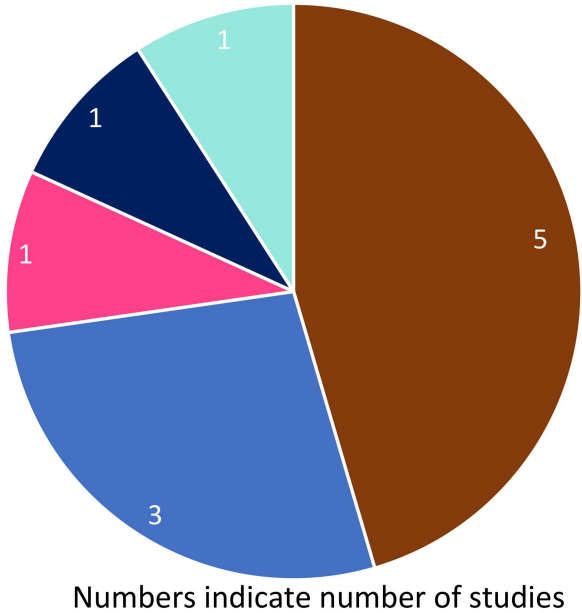
Legend – (A–C) mean standardized mortality ratios (SMRs) according to age, as reported by three studies from Thurman 2017 (Thurman et al. 2017); (D) SMR according to length of time since epilepsy diagnosis; (E) risk factors as reported using proportionate mortality ratios (PMR) categorized by epilepsy-type (symptomatic, undetermined,

cryptogenic), seizure-type (focal, generalized, unknown), and gender. Plots are in descending median order within categories; (F) hazard ratios (HR) in descending median order; (G) risk ratio; (H) mortality rate. The number of studies used to generate each box plot is shown in brackets on the x-axis. ^Cryptogenic includes idiopathic epilepsy. */O = outlier studies. Abbreviations: SMR = standardized mortality ratio; CP = cerebral palsy; MR = mortality rate; PWE = people with epilepsy; CI = confidence interval.

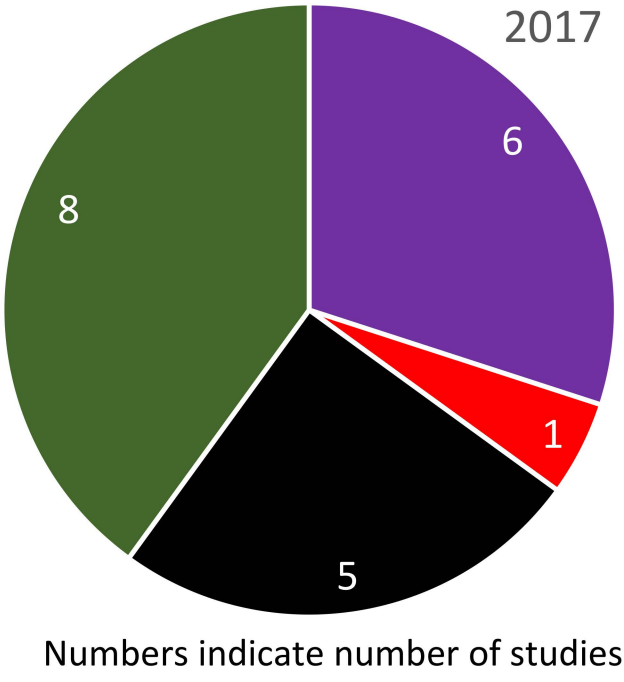

285 records identified through databases search (MEDLINE and Embase)
250 records removed as duplicates or irrelevent citations
35 potentially relevent records screened (titles, abstracts, full-text)
3 elligible systematic review found through hand-search of systematic review reference lists
23 records excluded:
8 systematic reviews of populations which may not necessarily have epilepsy
7 records were not systematic reviews
3 systematic reviews did not assess risk factors for the epilepsy-related death reviewed
2 systematic reviews of highly selected subpopulations
2 prior abstracts to included systematic reviews.
1 systematic review failed to identify any new studies
15 systematic reviews included - 6 contributing to the primary analysis and 9 contributing to the secondary analysis


A
B
C
D
E
F
Standardized mortality ratio
0
5
10
15
20
25
Levira 2017 (12)
Nevalainen 2014 (17)
Shackleton 2002 (15)
Thurman 2017 (19)
Watila 2018 (15)
Systematic review (no. of studies)
Pediatric (11)
Adult (18)
All ages (49)
Demographic groups: pediatric <18 years, adults ≥18 years, and all ages (no. of studies)
Hospital-based (32)
Community-based (46)
Source population: hospital- or community-based (no. of studies)
Incident cases (31)
Prevalent cases (38)
Both incident & prevalent cases (9)
Case selection: incident, prevalent, or both (no. of studies)
1930s (1)
1940s (1)
1950s (1)
1960s (3)
1970s (6)
1980s (4)
1990s (10)
2000s (24)
2010s (28)
Study publication year group (no. of studies)
Africa (4)
East Asia (6)
US & Canada (17)
Europe (43)
South Asia (3)
Central & South America (5)
Study continent (no. of studies)

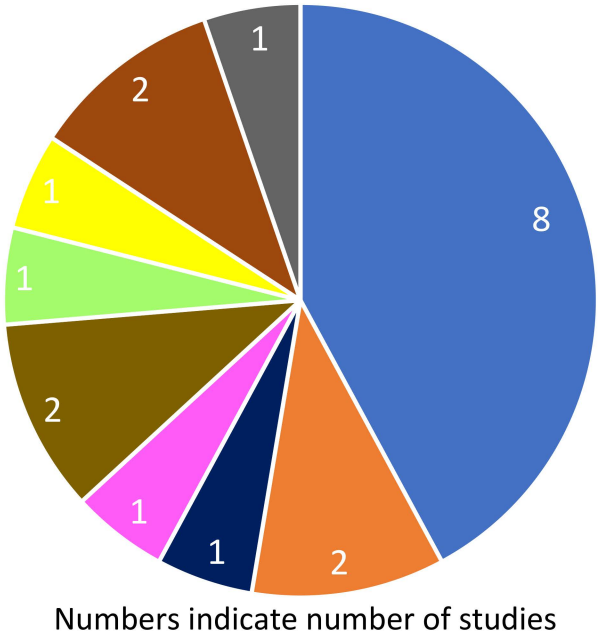
A

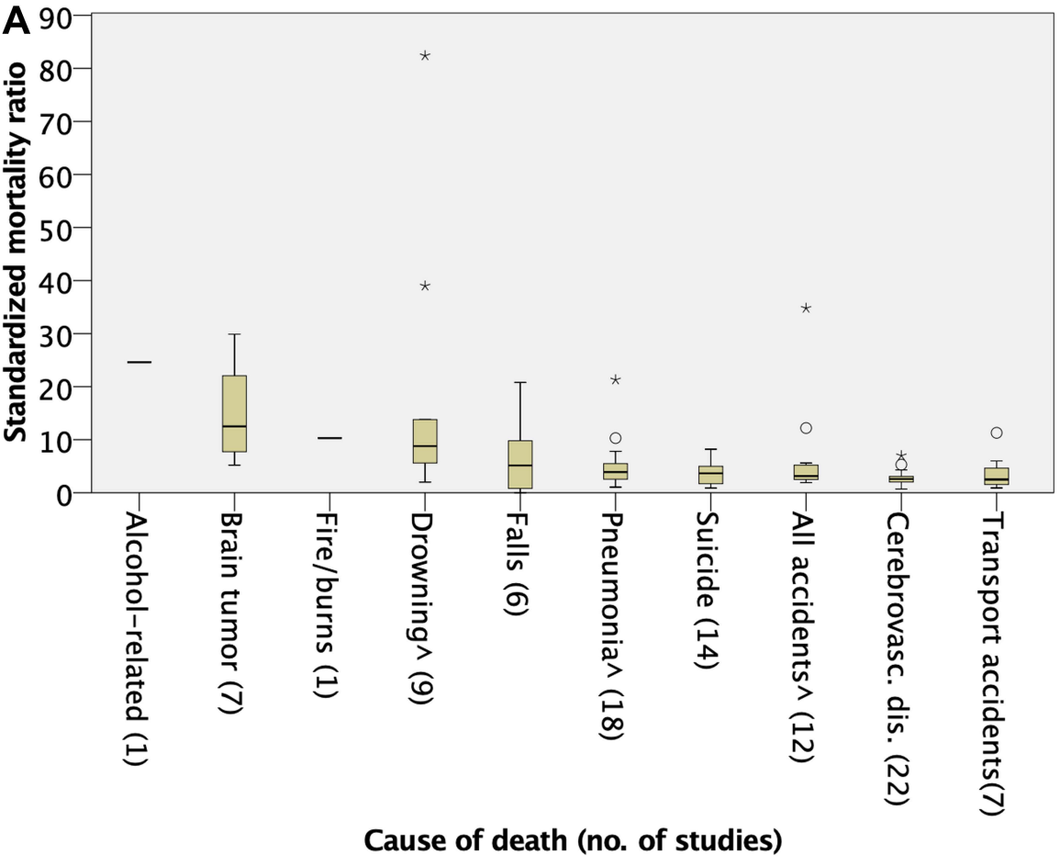

Source of cause of death information: Watila 2018
5
3
1
1
1
Death registries
Death certificates
Death certificates + post-morem
Death certificates + medical records + post-mortem
Death certificates + medical records + post-mortem + care-givers' report
Numbers indicate number of studies

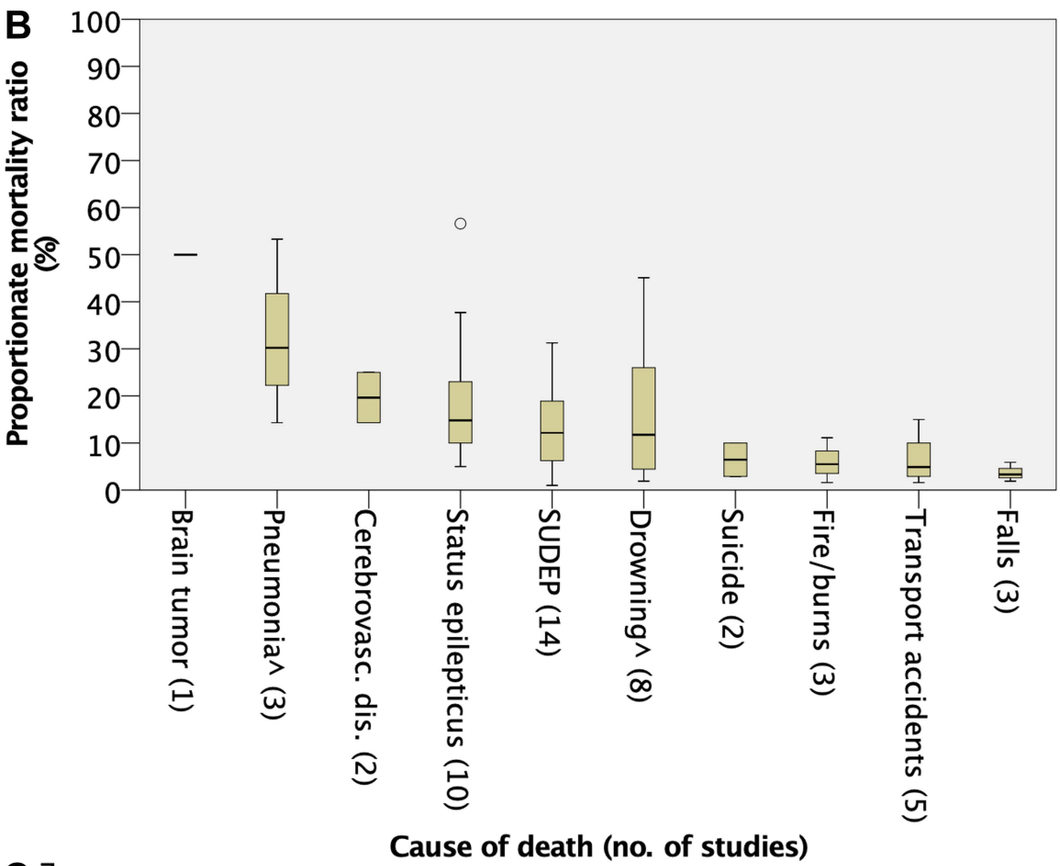
B

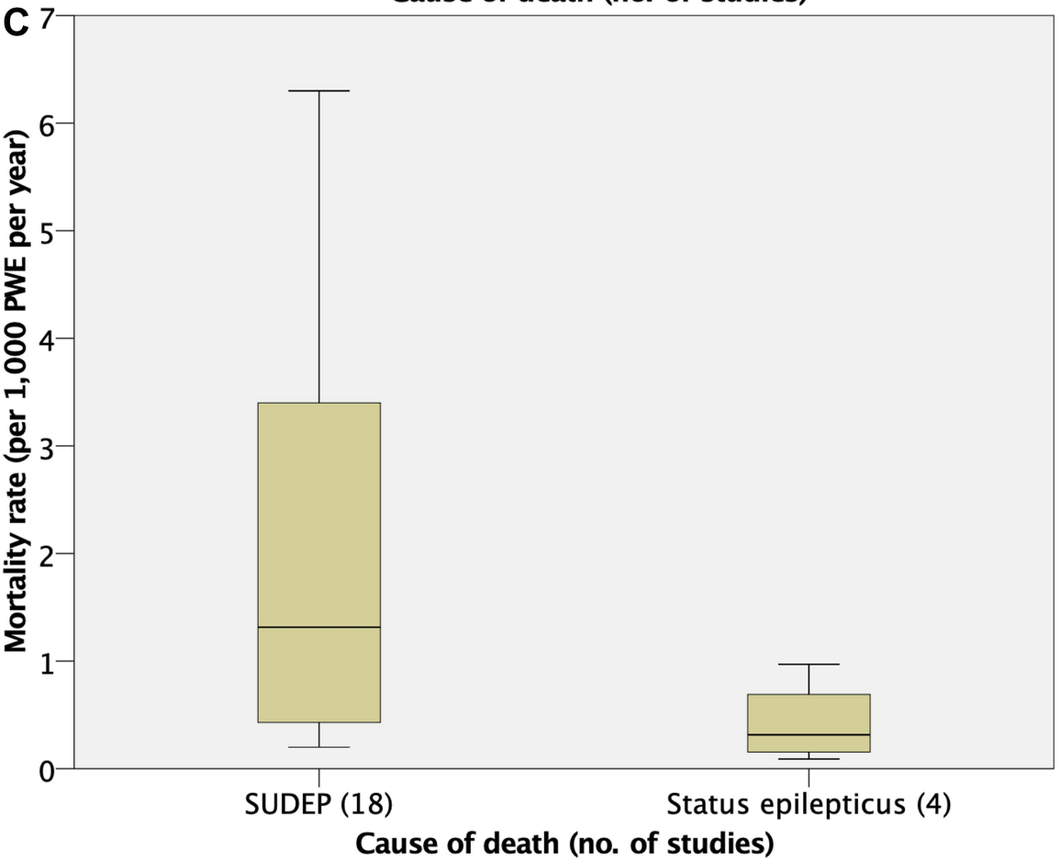

Source of cause of death information: Levira 2017
6
1
5
8
Verbal autopsies
Death certificate, hospital record &/or family doctor
Family reports
Source not reported or available
Numbers indicate number of studies

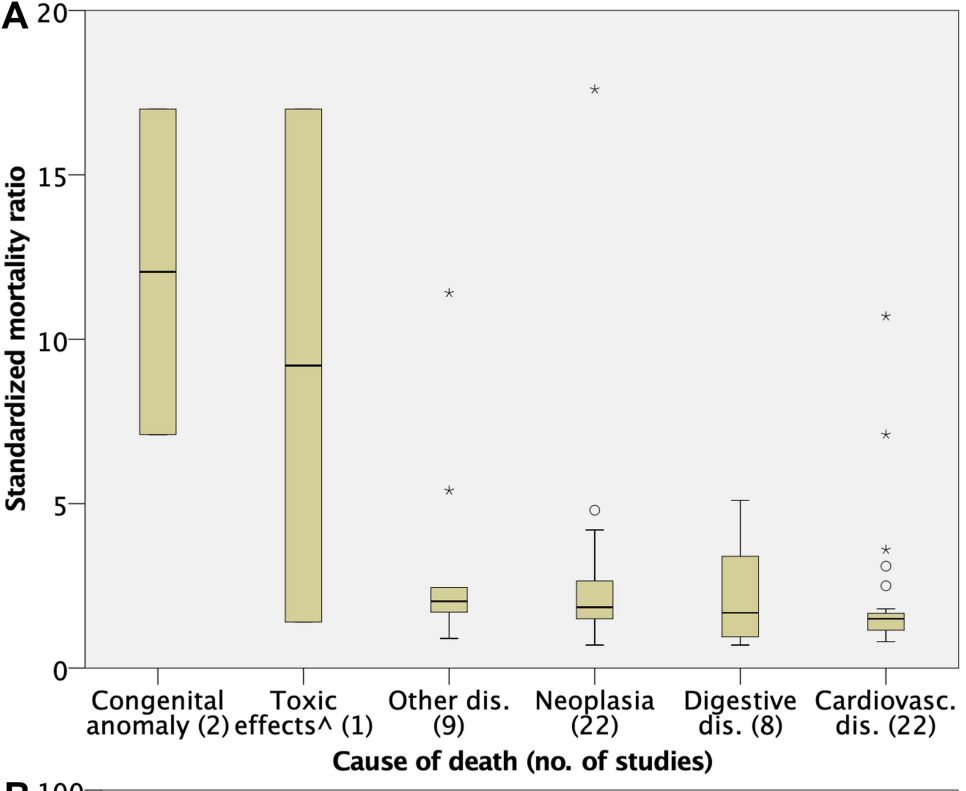
C

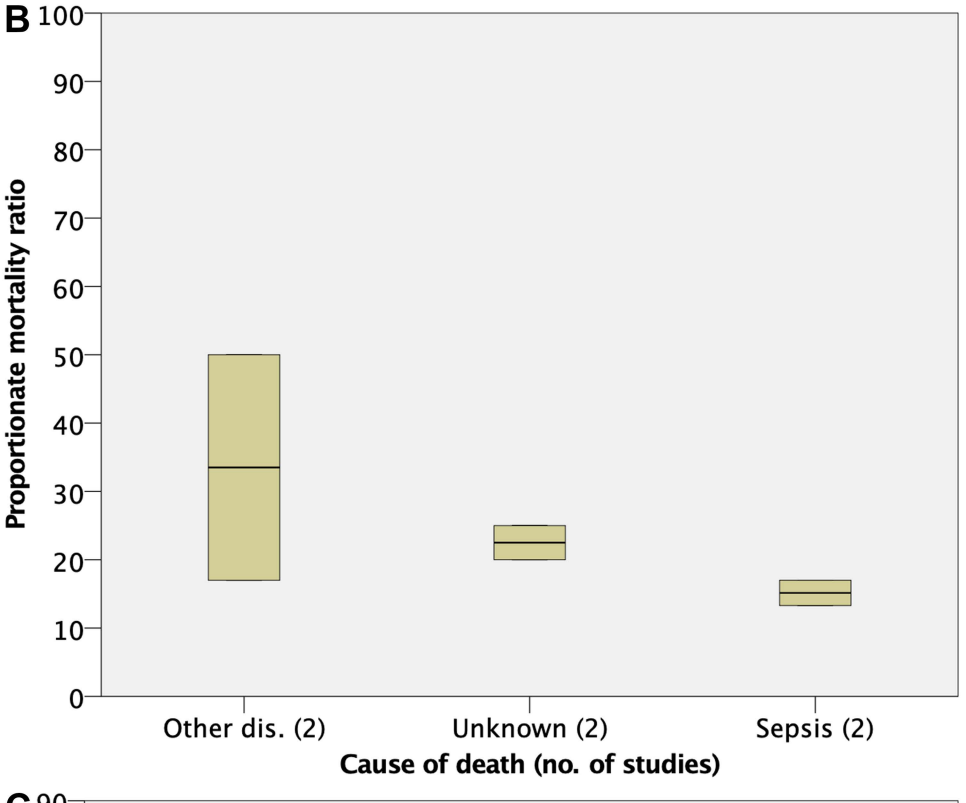

Source of cause of death information: Thurman 2017
8
2
1
1
1
2
1
2
1
Death certificates
Death certificates + medical records
Death certificates + medical records + post-mortem
Death certificates + medical records + post-mortem + family report
Medical records + post-mortem
Medical records + family report
Medical records
Death registries
Source not available
Numbers indicate number of studies

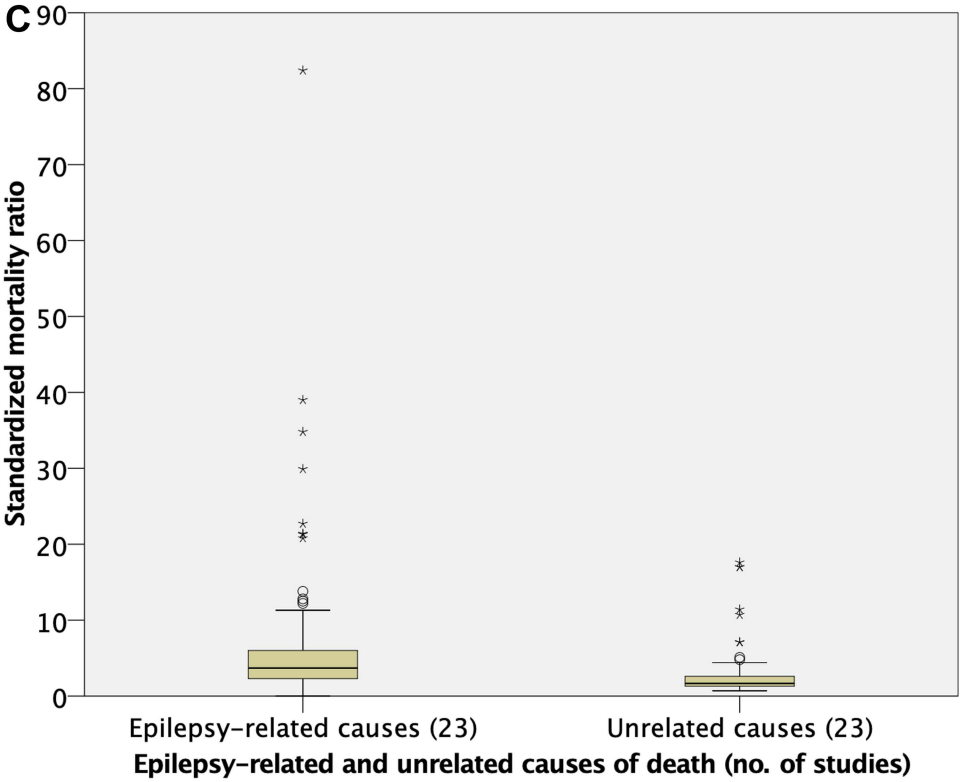

A
Standardized mortality ratio
90
80
70
60
50
40
30
20
10
0
Alcohol-related (1)
Brain tumor (7)
Fire/burns (1)
Drowning^ (9)
Falls (6)
Pneumonia^ (18)
Suicide (14)
All accidents^ (12)
Cerebrovasc. dis. (22)
Transport accidents(7)
Cause of death (no. of studies)


B
Proportionate mortality ratio (%)
100
90
80
70
60
50
40
30
20
10
0
Brain tumor (1)
Pneumonia^ (3)
Cerebrovasc. dis. (2)
Status epilepticus (10)
SUDEP (14)
Drowning^ (8)
Suicide (2)
Fire/burns (3)
Transport accidents (5)
Falls (3)
Cause of death (no. of studies)

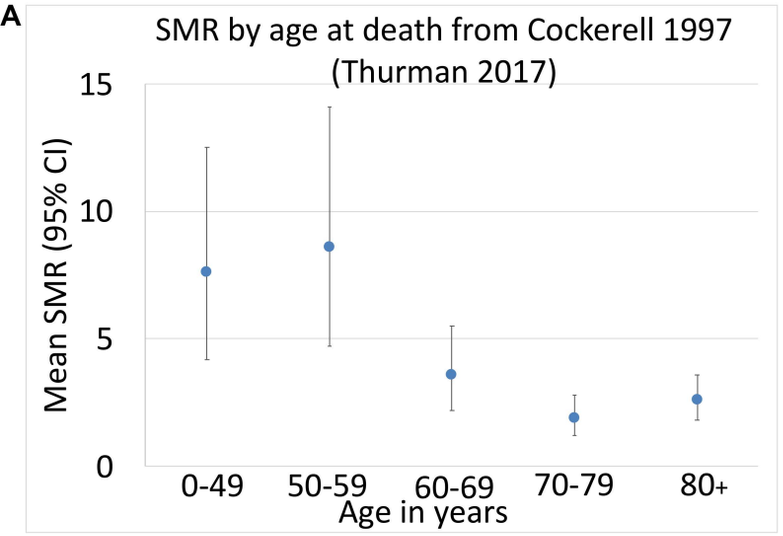

C
Mortality rate (per 1,000 PWE per year)
7
6
5
4
3
2
1
0
SUDEP (18)
Status epilepticus (4)
Cause of death (no. of studies)

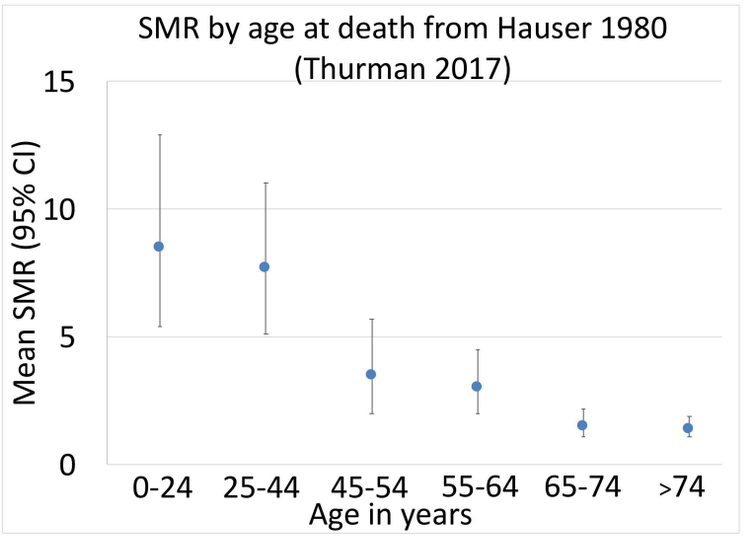

A
Standardized mortality ratio
0
5
10
15
20
Congenital anomaly (2)
Toxic effects^ (1)
Other dis. (9)
Neoplasia (22)
Digestive dis. (8)
Cardiovasc. dis. (22)
Cause of death (no. of studies)

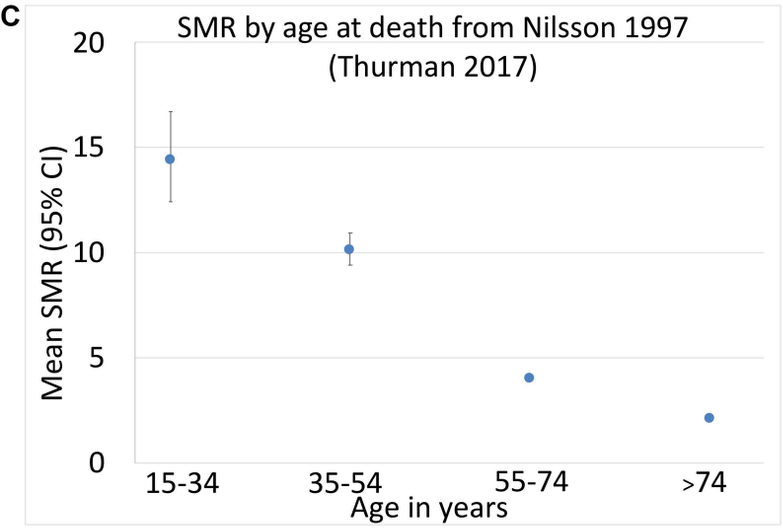

B
Proportionate mortality ratio
0
10
20
30
40
50
60
70
80
90
100
Other dis. (2)
Unknown (2)
Sepsis (2)
Cause of death (no. of studies)

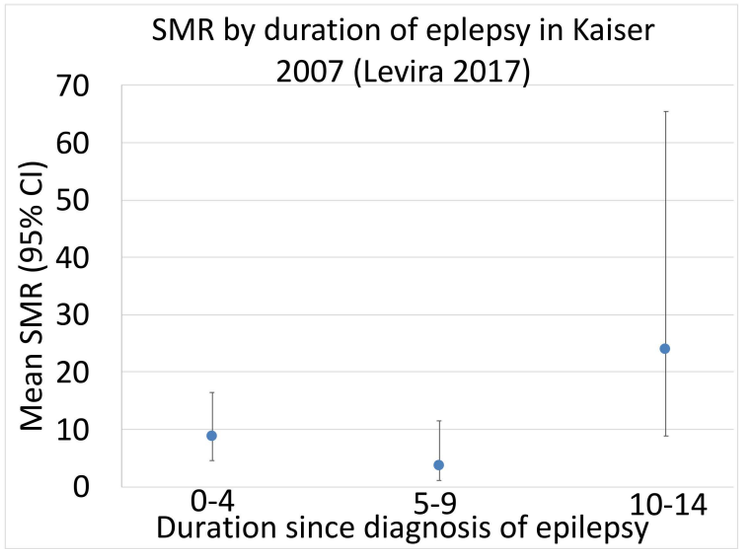

C
Standardized mortality ratio
0
10
20
30
40
50
60
70
80
90
Epilepsy-related causes (23)
Unrelated causes (23)
Epilepsy-related and unrelated causes of death (no. of studies)

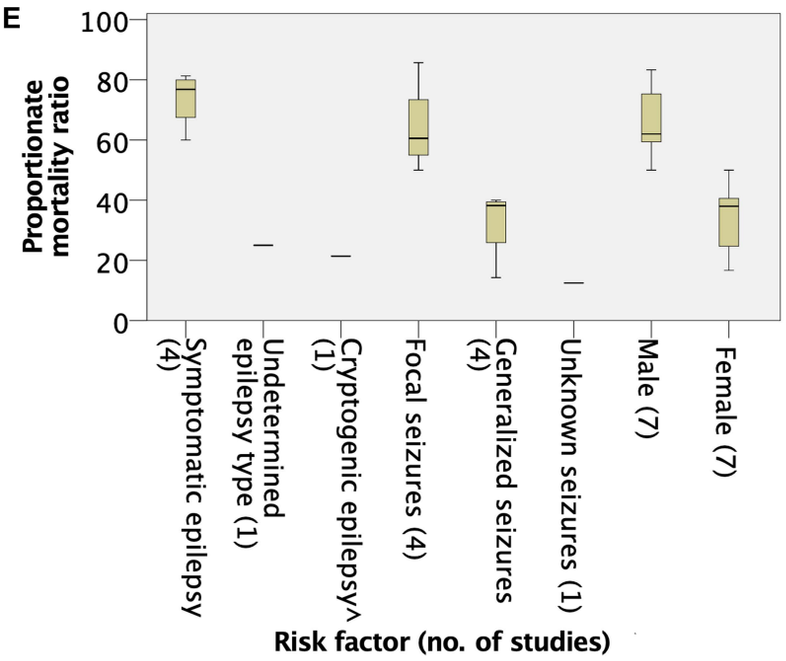
Standardized mortality ratio
0
5
10
15
20
25
30
35
40
45
50
55
Brain tumor (1)
Intellectual disability/CP (2)
Encephalopathies (6)
Dementia (1)
Cerebrovasc. dis. (1)
Congenital epilepsy^ (5)
Symptomatic epilepsy (21)
Undetermined epilepsy type (3)
Cryptogenic epilepsy^ (20)
Poor adherence^ (1)
Good adherence^ (1)
Childhood-onset^ (6)
Adult-onset^ (4)
Generalized seizures (3)
Focal seizures (3)
High seizure frequency^ (5)
Low seizure frequency^ (2)
Male (8)
Female (8)
Risk factor (no. of studies)

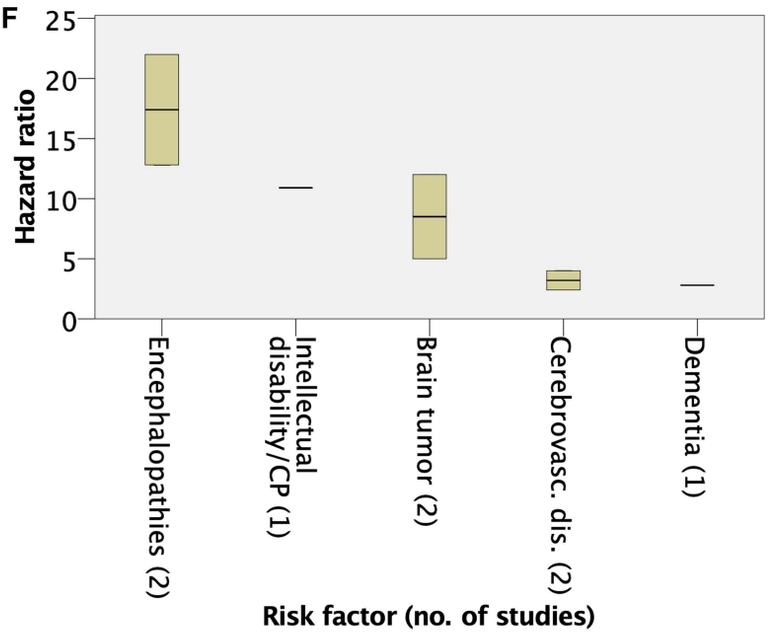

A
SMR by age at death from Cockerell 1997 (Thurman 2017)
Mean SMR (95% CI)
15
10
5
0
0-49
50-59
60-69
70-79
80+
Age in years

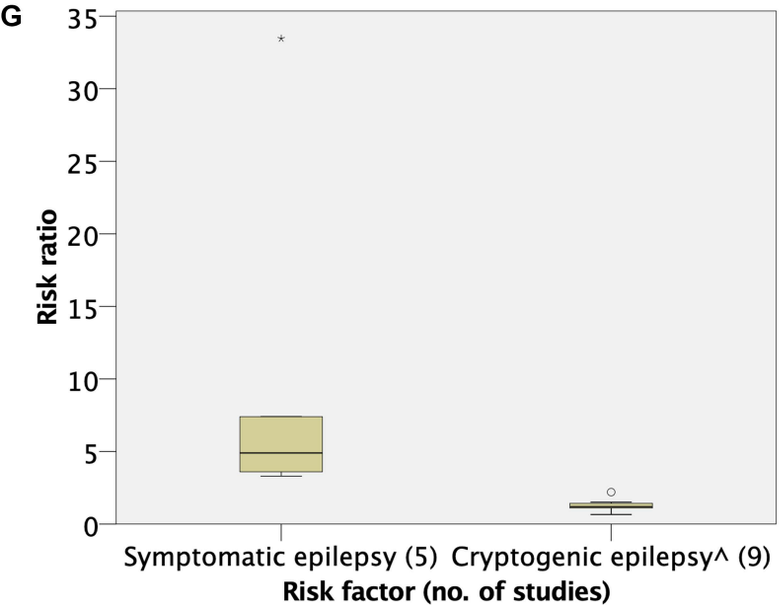

B
SMR by age at death from Hauser 1980 (Thurman 2017)
Mean SMR (95% CI)
15
10
5
0
0-24
25-44
45-54
55-64
65-74
>74
Age in years

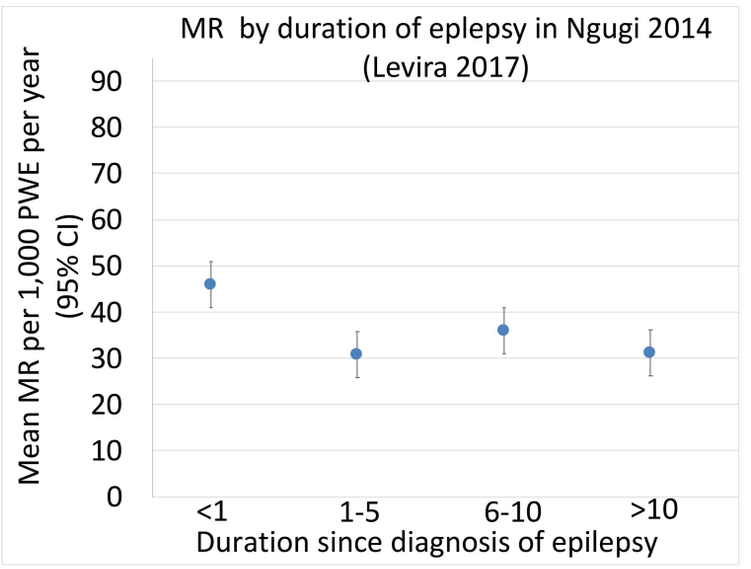

C
SMR by age at death from Nilsson 1997 (Thurman 2017)
Mean SMR (95% CI)
20
15
10
5
0
15-34
35-54
55-74
>74
Age in years


D
SMR by duration of eplepsy in Kaiser 2007 (Levira 2017)
Mean SMR (95% CI)
70
60
50
40
30
20
10
0
0-4
5-9
10-14
Duration since diagnosis of epilepsy


E
Proportionate mortality ratio
100
80
60
40
20
0
Symptomatic epilepsy (4)
Undetermined epilepsy type (1)
Cryptogenic epilepsy^ (1)
Focal seizures (4)
Generalized seizures (4)
Unknown seizures (1)
Male (7)
Female (7)
Risk factor (no. of studies)


F
Hazard ratio
25
20
15
10
5
0
Encephalopathies (2)
Intellectual disability/CP (1)
Brain tumor (2)
Cerebrovasc. dis. (2)
Dementia (1)
Risk factor (no. of studies)


G
Risk ratio
35
30
25
20
15
10
5
0
Symptomatic epilepsy (5)
Cryptogenic epilepsy^ (9)
Risk factor (no. of studies)


H
MR by duration of eplepsy in Ngugi 2014 (Levira 2017)
Mean MR per 1,000 PWE per year (95% CI)
90
80
70
60
50
40
30
20
10
0
<1
1-5
6-10
>10
Duration since diagnosis of epilepsy